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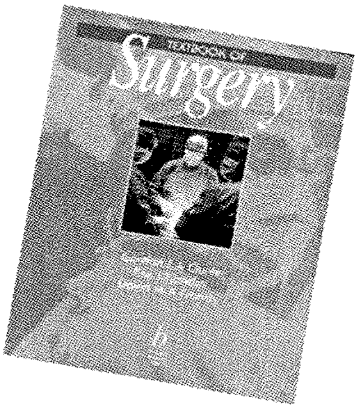

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A 5 day practical course designed for practitioners intending to introduce the laparoscopic approach to their institution.

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The practical course offers;

- "hands on" practical sessions
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- small group discussion with experts
- advice on avoidance of problems
- financial and management issues
- course workbook

Course fee includes accommodation, all meals and tuition materials

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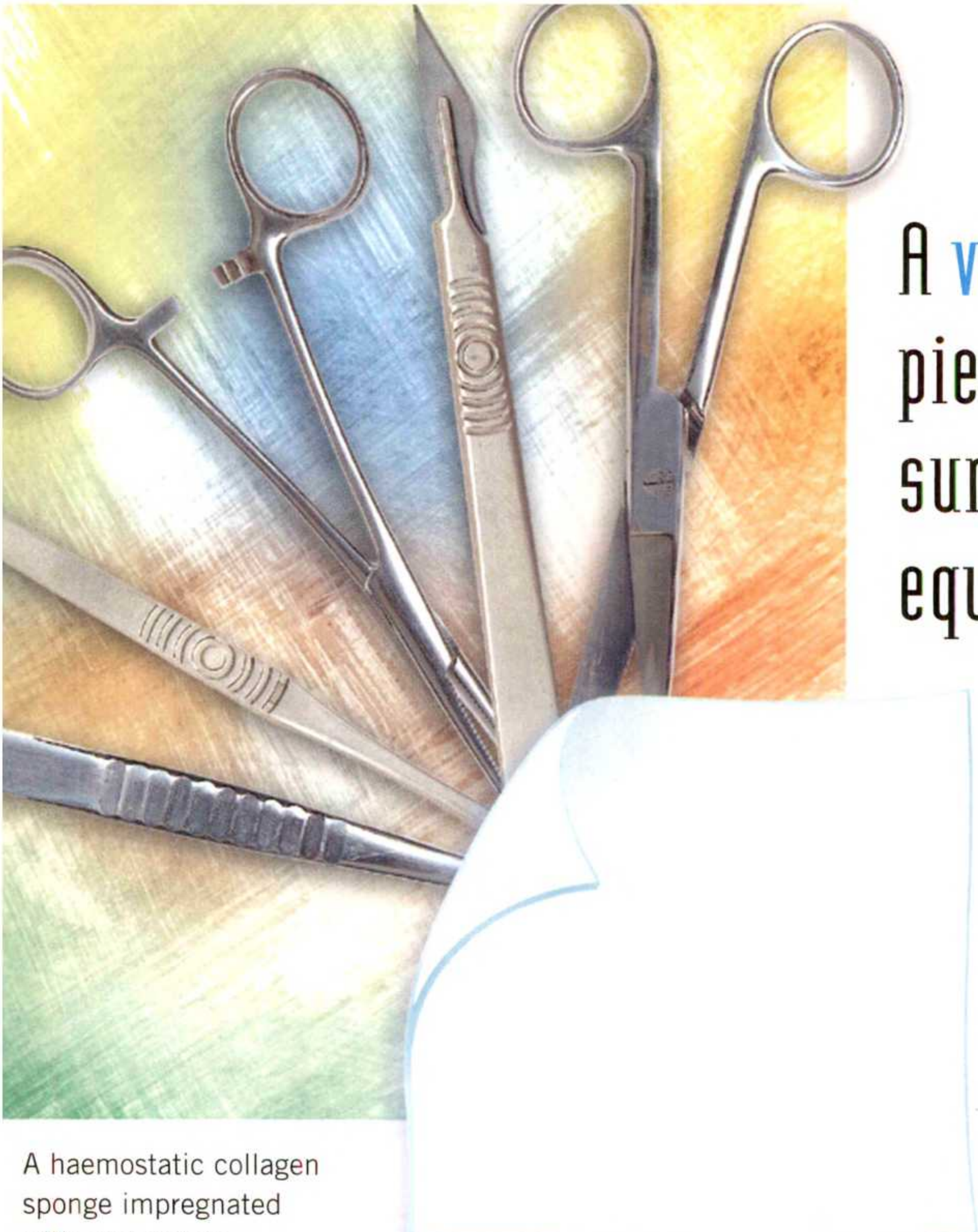

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british obesity surgery society

Preliminary meeting to establish the society at ASGBI May 1999 meeting in Brighton

Thursday 6 May at 6pm

(see program for venue)

There is an increasing need for a society to develop and maintain standards in this growing area of endeavour.

The Association of Upper GI Surgeons has agreed that a society should be established under it auspices. At the time above there will be a meeting to decide on an interim committee and constitution for a bariatric surgery society.

Please come to this meeting and have your say if you are interested in joining this new society.

The aims will be to:

- encourage regular sharing of experience
- establish an annual meeting
- develop a national database for audit and research
- promote the discipline to the public and funders
- provide advice and guard standards

For further information please contact:

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Leading article

Glutamine

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Recent interest in nutritional research in the critically ill patient has focused on key nutrients which, when ingested in excess of daily requirements, can modulate immune, metabolic and inflammatory processes. Of these nutrients, glutamine holds considerable potential to be the first to play a key role in the management of patients with critical illness.

Glutamine, a non-essential amino acid, occupies a central role in many metabolic pathways. It comprises more than 50 per cent of the body's free amino acid pool and is a precursor for synthesis of nucleic acids and glutathione. Glutamine is a 'nitrogen shuttle' between tissues and a fuel for enterocytes, colonocytes, lymphocytes and proliferating cells[1]. The function of the gut is impaired in patients with glutamine deficiency, particularly because of the loss of protection against the translocation of bacteria and/or endotoxin from the gut lumen into the portal circulation. In hypercatabolic states (stress, sepsis and trauma) plasma and intracellular glutamine concentrations fall. These decreases have been shown to be of prognostic value and correlate with patient survival.

In view of its central role, the effects of glutamine supplementation have been examined *in vivo* in patients with a variety of diseases. Beneficial effects have occurred in terms of maintenance of protein synthesis, a reduction in loss of body nitrogen following trauma, enhanced intracellular glutamine levels and stimulation of immune function[2]. Such metabolic and immunological benefits are encouraging and can be achieved by either enteral or parenteral administration, but at least 5 days of supplementation appears to be necessary. However, it is the effect of glutamine supplementation on clinical outcome that is important to the patient. In this era of evidence-based medicine, it must be asked what glutamine supplementation actually achieves in terms of hard clinical endpoints.

The ability of supplementation to prevent infectious complications and reduce hospital stay has been examined. In one study 28 patients undergoing elective operation for colorectal cancer received either glutamine-supplemented total parenteral nutrition (TPN) or isonitrogenous isocaloric TPN for 5 days after operation[3]. Patients receiving glutamine had a 29 per cent reduction in hospital stay. Looking critically at this study, however, it might be asked whether a mean stay of 22 days in the control group could be regarded as usual practice, particularly as no major complications occurred. Furthermore, the surgeon decided the time of discharge, criteria for which were not clearly defined, and factors that determined discharge included nursing considerations.

In a second study, 72 patients with multiple trauma (Injury Severity Score of 20 or more) received either glutamine-supplemented enteral nutrition or a diet with the same nitrogen and calorie content[4]. Again, glutamine supplementation was beneficial and there was a lower incidence of pneumonia in the 60 patients who received nutrition for at least 5 days (17 *versus* 45 per cent); bacteraemia and sepsis were also reduced. However, the duration of hospital stay was increased for glutamine-supplemented patients (*P* not significant) and the mortality rate was the same in both groups. In contrast, a further study showed a beneficial effect on mortality rate in patients with multiple organ failure who received parenteral glutamine supplementation. Although death was the endpoint of this study, this was at a time point of 6 months, and in the convalescent period factors other than glutamine may have been important[5].

The effect of glutamine in reducing infectious complications has also been examined in patients undergoing bone marrow transplantation[6]. Parenteral glutamine administration reduced both infectious complications and hospital stay by 20 per cent in 42 patients with haematological malignancy undergoing such transplantation. This effect of reducing hospital stay was confirmed in a smaller study of bone marrow transplantation[7]. However, in the latter study two patients in the glutamine group were excluded from the analysis, one dying from sepsis after 86 days in the intensive therapy unit and another from multiple organ failure after 10 days. Furthermore, although there was a trend towards a reduction in infectious complications, this was not statistically significant[7].

The ability of glutamine supplementation to improve absorption in the gastrointestinal tract has also been examined. In an uncontrolled trial involving patients with short bowel syndrome, intestinal function and absorption of nutrients were improved substantially by the administration of a combination of oral glutamine, growth hormone and a high-carbohydrate low-fat diet[8]. The rationale for using this combination was that growth hormone stimulates intestinal growth and the uptake of nutrients across the intestinal wall, and thus the modified diet allows maximal absorption of nutrients. Beneficial clinical effects occurred only when all three agents were given together. When a randomized controlled trial was carried out to investigate these effects further, the results were disappointing. In a small double-blind randomized placebo-controlled crossover study of eight patients with short bowel syndrome, the glutamine–hormone–diet combination resulted in only a modest increase in electrolyte absorption and delayed gastric emptying; there were no improvements in small bowel morphology, stool losses or absorption of macronutrients[9].

Glutamine supplementation may also play a role in protecting the gastrointestinal tract against chemotherapy-induced toxicity. Initial uncontrolled studies suggested that glutamine might reduce the severity of chemotherapy-induced stomatitis. A randomized controlled trial subsequently confirmed this beneficial effect of oral glutamine supplementation in lessening the severity and reducing the duration of stomatitis occurring during chemotherapy[10].

So what can be drawn from the studies that have addressed clinically important endpoints? It seems that glutamine does indeed reduce the risk of patients developing infectious complications after surgery and trauma, and it improves chemotherapy-induced stomatitis. However, whether these effects translate into a reduction in hospital stay and mortality rate remains unclear, and the role of glutamine and hormone combinations in the treatment of short bowel syndrome is also still unproven. Nevertheless, given the potential benefits outlined above, well designed clinical trials with clearly defined endpoints and adequate statistical power are urgently needed if the place of glutamine in clinical practice is to be confirmed.

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Thyroid surgery and the recurrent laryngeal nerve

Problematic clinical situations are discussed in the 'Clinical Dilemma' section. The Editors wish to encourage the BJS readership to play a part here. If you have a 'dilemma' which can be expressed as a question (not more than 40 words), please let us know by contacting the BJS office. You may even have thoughts on a suitable expert to voice an opinion. The most interesting problems will be followed up in this section of the Journal in the coming months.

In this issue of BJS a dilemma related to thyroid surgery is highlighted: what to do if the recurrent laryngeal nerve is difficult (or impossible) to find. How should this situation be handled? Professor Malcolm Wheeler of Cardiff replies.

It is a fundamental surgical principle that to avoid damaging any vital structure at operation that structure must be clearly identified by the surgeon. The recurrent laryngeal nerve (RLN) at thyroidectomy is no exception to this rule. However, it has not always been accepted that nerve identification is essential; Prioleau[1] considered it to be a dangerous practice to dissect the nerve saying 'It is an axiom in thyroid surgery that a recurrent laryngeal nerve seen is injured'. Others have since shown that routine dissection and identification of the RLN is a sound surgical practice which reduces the rate of nerve injury. Wade[2] demonstrated that this technique resulted in no permanent nerve injuries in 100 consecutive subtotal thyroidectomy procedures and suggested that if the RLN is injured when identified it is likely to produce only a transient palsy with eventual recovery. Adopting this strategy, RLN injury rates of zero have been reported even after total thyroidectomy for thyroid cancer[3].

What should the surgeon do if he cannot immediately identify the RLN at thyroidectomy? A meaningful and successful search demands a detailed knowledge of normal anatomy and an awareness of the common variations in nerve location. Only rarely is the nerve actually in the tracheo-oesophageal groove and, furthermore, the right nerve has a more oblique course in its lower third and is a greater distance from the trachea than its contralateral partner. Identification may be assisted by palpation; the nerve feels like a cord which can be rolled against the trachea. This can direct gentle dissection with a fine jaw haemostat to open the fascial layers along the line of the nerve and expose the structure. It may be recognized as a glistening white cord with a fine accompanying artery. Its visualization throughout the remainder of its course requires careful dissection, particularly in the region of the inferior thyroid artery, with precise delineation of the variable nerve/artery relationship; the nerve usually lies at a deeper level.

If the RLN has still not been identified with certainty at this stage, attention should be focused on the upper third of its course where it passes deep to or through the layers of the ligament of Berry to enter the larynx. The nerve is at great risk here and its exposure requires careful division of the superficial layers of the fascia using fine haemostats to pick up the tissue, staying close to the thyroid and being absolutely certain at each stage that only fascia and small arterial branches are divided. One must emphasize that the nerve may take a curved looping course which renders it particularly vulnerable in this region. Palpation of the inferior cornu of the larynx is a most valuable aid to nerve identification, reliably indicating the point of its entry into the larynx[4]. This is especially relevant if the nerve has not been identified in the lower part of its course.

In this worrisome and dangerous scenario of the unidentified RLN, the surgeon should be aware of the close relationship it may have with thyroid nodules. The nerve never pierces the capsule of the thyroid gland itself, but it is not uncommon for tunnelling amongst thyroid tissue to occur owing to the irregular growth of thyroid nodules. Large goitres, especially when retrosternal, have a remarkable ability to displace the nerve. Anterior fixation to the thyroid gland in a vascular fork of the inferior thyroid artery is also an important circumstance which may endanger the nerve. Finally, the RLN has a propensity to divide into two or more branches which may also serve to confuse. All of the above are worthy of serious consideration when the nerve is not easily located.

On the right side of the neck the RLN may be non-recurrent[5] and pass medially with the inferior thyroid artery; this anatomical variation may cause difficulty in identification. It is rarely necessary to ligate the main trunk of the inferior thyroid artery during thyroidectomy, but it is evident that such ligation would render a non-recurrent nerve extremely vulnerable to damage. A non-recurrent nerve is rare on the left side but it may occur in patients with situs inversus and in situations of vascular anomaly.

In circumstances in which nerve identification is still in doubt, the technique of staying close to the thyroid capsule and dividing small terminal arterial branches on the surface of the gland should ensure a safe thyroidectomy with preservation of parathyroid blood supply and minimal risk of nerve injury[6]. This technique of capsular dissection may be particularly appropriate for the scarred and distorted neck, so often encountered during reoperative thyroidectomy even for benign disease, where nerve identification may be virtually impossible. However, for primary thyroidectomy, if due attention is given to meticulous haemostasis and dissection in a bloodless field, there should be few, if any, instances in which the RLN cannot be identified.

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Interstitial laser coagulation for hepatic tumours

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Background: The potential role of interstitial laser coagulation (ILC) for patients with irresectable hepatic tumours is currently being investigated. Since its introduction in 1983 it has evolved into an innovative minimally invasive technique.

Methods: On the basis of a Medline literature search and the authors' experience, the principles, current state and prospects of ILC for hepatic tumours are reviewed.

Results: Animal studies and early clinical studies have shown the safety and feasibility of ILC. The site of interest can be approached at laparoscopy or percutaneously and treatment is easily repeatable. Recent advances include the use of fibres with a cylindrical diffusing light-emitting tip, the length of which is adaptable to tumour diameter, water-cooled fibre systems, simultaneous multiple fibre application, and hepatic inflow occlusion during laser treatment. ILC allows complete destruction of tumours up to 5 cm in diameter. Currently a limitation is the lack of reliable real-time monitoring of laser-induced effects but progress in magnetic resonance imaging techniques should allow accurate temperature measurements to be obtained rapidly during treatment. However, the actual benefit of ILC in terms of patient survival remains to be investigated.

Conclusion: In terms of tools and experience, ILC has now been developed sufficiently to study its effect on survival of patients with irresectable hepatic tumours.

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Surgical resection of primary and secondary hepatic tumours leads to an improved 5-year survival rate of 20–40 per cent[1]. The majority of patients with hepatic metastases of colorectal carcinoma, however, do not fulfil the criteria that justify partial hepatectomy[2–4]. Resection of hepatocellular carcinoma (HCC) in cirrhotic liver is restricted even further by the high operative risk associated with the poor general status of the patient and/or the reduced functional hepatic capacity[5]. In the past 10 years the introduction of screening programmes has resulted in a relative increase in the number of resectable cases; the absolute number patients for whom no treatment is available has also increased[5,6].

Alternative therapies have been developed for the treatment of hepatic malignancies, aimed at local, regional or systemic treatment. As segmental and even subsegmental resections may yield results akin to those of larger partial hepatectomies[7–9], provided the resection margin is free from tumour cells, there is a rationale for local tumour destruction. Furthermore, on theoretical grounds, stimulation of dormant malignant cells may be less when using local approaches[10,11]. In general, the various local techniques using physical means (cold, heat or dehydration) lead to instant cell death. Cryosurgery, alcohol injection, radiofrequency coagulation and focused ultrasound are currently being investigated and have been reviewed in recent articles[12–14]. Overall, their widespread clinical application has been hindered by ineffective or unpredictable tumour destruction or by hepatotoxicity[15].

Interstitial laser coagulation (ILC), introduced in 1983 by Bown[16], has matured in recent years. ILC is a thermal technique aimed at coagulation of solid tumours by local light delivery using thin flexible fibre(s) (*Fig. 1*). Early experimental findings have been confirmed in preliminary clinical case series, as reported earlier in this journal[17,18]. While the ILC procedure itself was judged feasible and tolerable, improvement in the technique was necessary for its successful application to tumours larger than 2·5 cm in diameter. In this review the background, recent progress and future perspectives of ILC are discussed with regard to the treatment of hepatic tumours.

Methods

A Medline search (OVID Technologies 3.0, New York, USA) was carried out for the period from 1983 to the present using the textwords 'laser', 'liver' and 'interstitial'. Furthermore, relevant papers were identified from the reference lists of the papers previously obtained through the Medline search together with abstracts from recent international meetings. Papers describing clinical studies were included only if (1) the tumour response rates were stated and (2) complications were described.

Laser–tissue interaction

ILC uses laser light at low power (3–15 W) with long exposure times (3–20 min), resulting in coagulation, noted as blanching of the tissue as in a boiled egg (*Fig. 1*). The treated area is left to undergo necrosis *in situ* with subsequent healing by regeneration and/or fibrosis. The volume of tissue destruction is a function of both fibre position(s) within the tumour, and the temperature gradients created by the amount of power and duration of exposure. The subsequent biological response to laser light depends on the interaction of the light with the tissue[19]. On absorption of the laser light several thermal effects occur (*Table 1*). Coagulation is defined as the irreversible thermal damage of tissue proteins at temperatures between 55 and 95°C.

The compromise between deep penetration of the laser light and sufficient absorption in the tissue determines the optimal wavelength for ILC. Neodymium yttrium–aluminium–garnet (Nd YAG) (wavelength 1064 nm) and diode light (890 nm) have been investigated[23–25]. Both wavelengths are minimally absorbed by water and depend on tissue chromophores for their effect. Nd YAG light penetrates the tissue up to 10 mm from the light source[19].

As tumour and liver differ in colour, their optical characteristics might also differ. Van Hillegersberg *et al.*[26] found no net difference in absorption coefficient between rat tumour and liver at 1064 nm; scattering was only slightly greater in tumour. More important are changes in optical characteristics in the process of coagulation (during

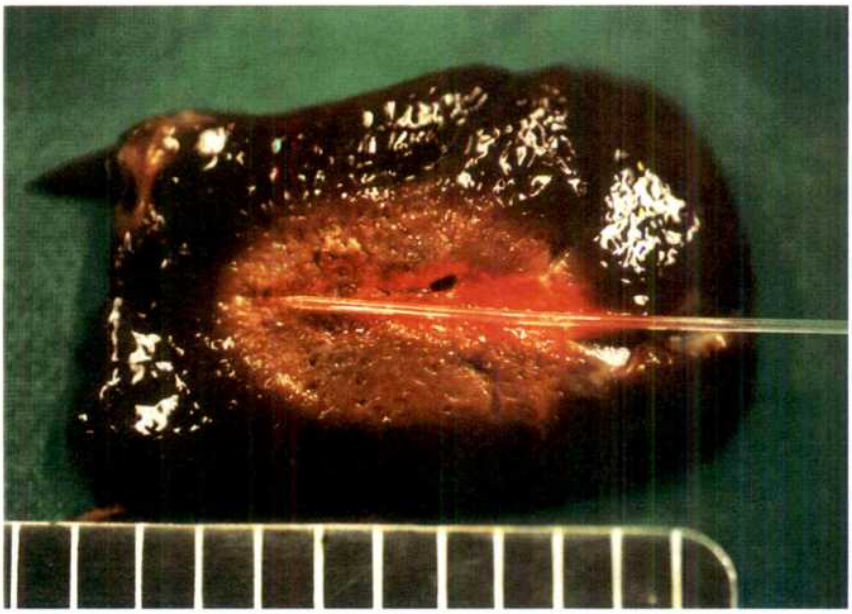

Fig. 1 Coagulated lesion in *ex vivo* pig liver. After laser treatment (6 W during 6 min (2160 J) of neodymium yttrium–aluminium–garnet light) the liver was sectioned in the plane along the laser fibre which is *in situ* (0·9 mm in diameter with a cylindrical diffusing tip of 2 cm). The whitish region is the resulting area of coagulation (maximum length 36 mm, diameter 26 mm)

Table 1 Tissue temperature and effects

Temperature (°C)	Physical effect	Biological effect
40–45	Heating	Enzyme inactivation
60–140	Protein denaturation	Cell shrinkage, hyperchromasia, membrane rupture, pyknosis, hyalinization of collagen
100–300	Water vaporization	Extracellular steam vacuole and cell shrinkage
300–1000	Carbonization and ablation	Ablation vaporization and carbonization

From Thomsen[20], Hunter and Dixon[21] and Welch *et al.*[22]

laser treatment). Light measurements during laser treatment of a tumour implanted in rat liver showed that light uptake increased, suggesting that absorption in the coagulated area decreased and light penetration increased[27]. This has recently been confirmed by determination of the optical characteristics of vital and coagulated tissue[28].

Both increasing power and increasing exposure time result in an increase in the area of coagulation; power is the most important factor[29,30]. Eventually, lesion size is limited at a plateau owing to decreased light density and conducted heat at the tissue peripheral to the laser fibre[31].

Interstitial laser fibres

With the use of a conventional bare-tip fibre, where light emission is concentrated at the tip, carbonization occurs. The blackish tissue limits the penetration of light to the surrounding tissue resulting in local temperature accumulation[22]. As a consequence, the temperature profile from a carbonized tip is no different from that of any other type of hot tip; one might as well use a hot knitting needle. With cylindrical diffusing fibre tips homogeneous light emission is produced over the entire light-diffusing length, as seen in *Fig. 1*, allowing the emitted laser light to be distributed equally throughout the surrounding tissue[31]. It was initially thought that carbonization was necessary to create a large lesion[25,30,32]. However, at the optimal combination of exposure time and laser power, light-diffusing tips result in larger lesions with less inter-lesion variation[29,33]. Recent years have seen major improvements in the quality of the diffusing tip fibres, resulting in better flexibility and thermoresistance. In addition, the length of the diffusing tip can be adapted to tumour diameter[29,34].

As the eventual coagulation size that can be produced with a single fibre is limited, simultaneous multiple fibre application has been used for lesions greater than 2 cm in diameter[35,36]. Owing to a synergistic effect between the fibres, a fourfold to sixfold increase in lesion volume occurs[37], resulting in areas of coagulation 5 cm in diameter[38]. Both reduced heat dissipation in the centre of the fibres and an additive effect at the borders of the individual lesions account for this effect[35]. For this purpose several beam-splitting devices have been developed so that a single laser machine can feed multiple fibres[17,39,40]. In studies in *ex vivo* porcine liver a discrete optimal mutual fibre distance (2 cm) for the maximal synergistic effect was found (lesions with a diameter of 5 cm[38]). The importance of the mutual fibre distance is illustrated by the finding that smaller distances between the fibres resulted in smaller lesions with central carbonization, whereas larger distances resulted in multiple separate zones of coagulation.

The latest development is a closed catheter system, transparent to laser light, through which a diffusing tip is introduced into the tissue[41]. The catheter is irrigated with water during laser treatment. This produces a temperature reduction at the surface of the catheter, allowing the exposure time and power to be increased without the risk of carbonization and fibre destruction. Lesions up to 5 cm in diameter can be created when used in combination with diffusing tips of 4 cm[42]. The insertion of one fibre into a tumour is more precise than the positioning of four fibres at an equal depth and discrete mutual distance. However, as the closed catheter system is larger in diameter (1·6 *versus* 3 mm) flexibility is reduced and the risk of haemorrhage in the tract to the target may be increased.

Histopathological evidence of effect

Thermal protein denaturation results in macroscopic tissue whitening but this is not a good indicator of the exact outer boundary of the lethal tissue effect. Under light microscopy the borders of a coagulated lesion show a rim consisting of haemorrhage, hyperaemia and oedema[43,44]. This haemorrhagic zone is a typical finding after laser coagulation in a variety of tissues and is explained by thermal intravascular erythrolysis[43]. The cells of the zone are devitalized as shown by loss of mitochondrial enzymatic activity[45].

Morphological observations using light microscopy do not allow unambiguous conclusions about the cell viability in coagulated tissue immediately after treatment. Cells with a nucleus have been described in haematoxylin and eosin-stained biopsy specimens following ILC, which were found to be non-vital when studied with electron microscopy[46]. With immunohistochemical methods the authors' group and others have ruled out the presence of vital cells in animal models with and without tumour, using either localization of nicotinamide adenine dinucleotide metabolism directly after ILC treatment[45,47] or by 5-bromo-2′-deoxyuridine incorporation 6–36 days after ILC (*Fig. 2*)[27,48]. Complete cell death has also been confirmed in laser-induced coagulation in the resection specimens of patients with hepatic metastases who underwent resection 2–3 days after ILC[49].

Notwithstanding the difficulties in defining coagulation damage, a rough outline can be given. In essence, no difference in reaction between tumour and normal tissue has been found. The acute lesion has a characteristic zonal architecture as described in detail in the literature[27,50,51]. Briefly, in a central zone surrounding the insertion of the laser probe the gross tissue structure is well preserved, whereas cellular build-up is characterized by acidophilic

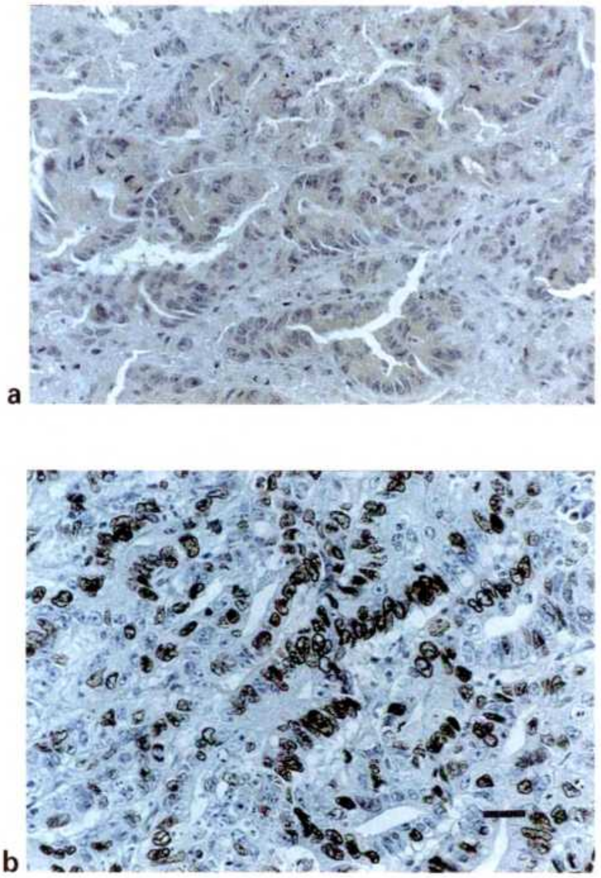

Fig. 2 5-Bromo-2′-deoxyuridine (BrdU) histochemistry of CC531 tumour in rat liver 36 days after laser or sham treatment. **a** The nuclei of the coagulated tumour in the degenerative core do not label with anti-BrdU, a marker of proliferating DNA. **b** Strong labelling in the cellular nuclei of a tumour in a sham-treated animal (bar 15 μm). Haematoxylin and eosin stain. (Reproduced with permission from R. van Hillegersberg. Laser treatment for hepatic metastases: thermal and photodynamic therapy. *Thesis*, Erasmus University, Rotterdam, 1993)

cytoplasm and elongated nuclei (*Fig. 2a*). In liver tissue this zone is surrounded by a broad area, containing dilated sinusoids and cells with vacuolated cytoplasm. The outer, macroscopically detectable, haemorrhagic zone consists of cells with less vacuolated cytoplasm and hyperaemic sinusoids.

In the process of regeneration, a fibrotic rim is formed delineating normal tissue from the coagulum, which can be palpated as a dense mass. This process of regeneration is a mesenchymal reorganization with proliferation of fibroblasts, endothelium and bile ducts[17,27,52,53]. The original tissue architecture remains intact with no ingrowth of blood vessels inside the fibrotic rim. Depending on initial size, complete regeneration of hepatic tissue takes place between 3 and 12 months after laser treatment, as demonstrated in normal liver of rabbits[52], dogs[17] and pigs[53].

Studies in experimental animal models

Studies in animal models have been performed using tumour-bearing rodents[27,54] and rabbits[55,56], as well as in rodents[57,58], dogs[17] and pigs[44,45,48,59–61] with normal livers. In the tumour models the cytotoxicity of ILC was studied; the normal-liver models allowed strategies to increase coagulation volume at human scale to be investigated.

The earliest documented work was by Matthewson *et al.*[62] in rat liver using Nd YAG light. A 0·4-mm diameter fibre was inserted into the centre of a lobe of liver, exposed at laparotomy. Power settings of 0·5–2 W and exposure times of 50–2400 s were used to give well defined lesions of coagulative necrosis with sharp boundaries between normal and coagulated liver. The size of coagulation increased with increasing laser energy until a plateau was reached. Van Hillegersberg *et al.*[27] studied ILC in a rat liver tumour model. Lesion size and liver enzymes increased with laser energy applied. Deterioration in liver function was not found. At optimal laser settings complete tumour eradication was obtained. In addition, several rodent models with subcutaneous implanted tumours showed the tumour cell killing potential of ILC[63,64]. Recently an indication of reduced outgrowth of remnant tumour has been found after ILC compared with resection in liver tumours in rats[65].

In a second phase of animal experiments, modifications to enlarge the volume of coagulation were studied in large-animal models. Steger *et al.*[17] used dogs to evaluate the use of a laser beam-splitting device to feed four fibres at a mutual distance of 1·5 cm which resulted in lesions of 3·5 cm maximum.

A second line of investigation was to evaluate the influence of hepatic blood flow on the magnitude of the coagulation. Computer simulations[66] and mathematical modelling[67] predicted a fourfold to fivefold increase in the area of coagulation in liver without blood flow. The relatively small size of previous animal models and the small volume of coagulation that could be produced had obscured such an effect. These predictions were confirmed independently by three research groups, using multiple[44,45] and single[48] fibre application in pigs. With physiological blood flow through the liver, the volume of coagulation is reduced to 10–20 per cent and tissue is preserved around large vessels[52,68]. Germer *et al.*[45] and Möller *et al.*[48] investigated complete occlusion *versus* physiological flow, and the authors' group also differentiated between portal inflow occlusion only *versus* complete inflow occlusion (arterial and portal). It was found that portal inflow occlusion suffices to overcome the cooling effect of the blood flow[44]. Although it is generally assumed that hepatic metastases are mainly supplied by the arterial tree[69], clamping of both hepatic artery and portal vein is unlikely to be needed in the clinical situation. The poorly organized vascular bed in the tumour will probably cause only minimal tissue cooling and thus minimal lesion reduction[70]. Furthermore, in the often ischaemic centre of the tumour, in particular, little extra effect can be expected from eliminating the arterial blood flow. However, the tumour is surrounded by well perfused liver parenchyma and it is here that the cooling effect is mainly exerted[71]. Therefore, eliminating portal blood flow should enhance the destruction of the vital rim of the tumour and a margin of normal liver tissue. Also portal inflow occlusion alone, through a percutaneous transhepatic route[72,73], is less invasive than methods of achieving total arrest of blood flow. In a recent experimental study in pigs, the authors investigated the effects of ILC in the liver with portal inflow occlusion with a long-term follow-up[53]. No adverse events occurred, even in the vicinity of large vessels situated centrally in the liver. For ILC of primary liver cancer, portal inflow occlusion may not be needed in a cirrhotic liver, as the portal flow is often negligible or even retrograde. In this situation the magnitude of the arterial flow should be considered as a potential cooling source.

Treatment monitoring and evaluation

Currently, ILC is limited by the lack of reliable real-time monitoring of laser-induced effects. Ideally, real-time monitoring of ILC should provide information about the extent of coagulation in relation to the anatomy of the liver during treatment. The intervention may then be prolonged to ensure complete coagulation of the entire tumour, or terminated to prevent damage to vital structures. Interstitially placed thermosensors and light detectors for precise measurements are of little use because of the limited number of sample points and the extra trauma associated with their placement. It is likely that real-time monitoring by a non-invasive imaging technique is the key to control ILC. Several such techniques have been investigated.

Ultrasonography

Ultrasonography enables accurate placement of catheters into the tumour. Real-time imaging of the treated area has also been investigated but the echogenic area that is observed during coagulation does not correlate with the coagulative damage[48,74,75]. The image is caused by formation of bubbles from evaporated tissue water. Ultrasonography is also not helpful in evaluating lesions after treatment as the echogenic area becomes heterogeneous within minutes[75,76].

Computed tomography

For the diagnostic assessment before treatment, triphasic spiral computed tomography (CT) is indicated to define the number, location and dimensions of metastases before therapy. Contrast-enhanced CT after treatment shows the result of laser treatment very clearly as a well defined, non-enhanced area, easily distinguishable from the untreated, thus vascularized, enhancing tumour areas (*Fig. 3*). Contrast-enhanced triphasic CT after laser treatment should be considered as the evaluative 'gold standard'. The optimal time to perform ILC after CT is between 1 and 4 days, which corresponds with the time at which experimentally induced coagulated lesions have their maximum diameter. Unfortunately, after longer intervals CT cannot differentiate between inflammatory change, regenerating liver or recurrent tumour. Because of the radiographic load and insensitivity to soft tissue changes, there is no role for real-time CT during ILC.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is not restricted solely to morphology; physiological parameters may also be measured. Initial experience in monitoring laser treatment in patients with hepatic metastases consisted of conventional T1-weighted imaging[77–79]. These T1-weighted sequences are available on all clinical systems and do not require advanced computer-assisted image interpretation. The temperature dependence of T1 has been demonstrated *in vitro* for several biological systems[80]. However, the relationship between T1 and temperature is not simple because of the multifactorial nature of T1[81,82]; the temperature dependence of T1 also varies strongly for different types of tissue[81]. Furthermore, precise measurements of the absolute value of T1 are difficult[83]. Gewiese *et al.*[84] visualized a laser heated region, in *ex vivo* tissue, as a bright area surrounded by a dark border which was found to correspond with an isotherm of 45°C (20°C increase from starting temperature). More subtle differences, however, were undetectable. Therefore the current status of T1-weighted monitoring of heat deposition in tissue does not represent adequate thermometry.

The change in the proton resonance frequency (PRF) represents an alternative temperature-dependent magnetic

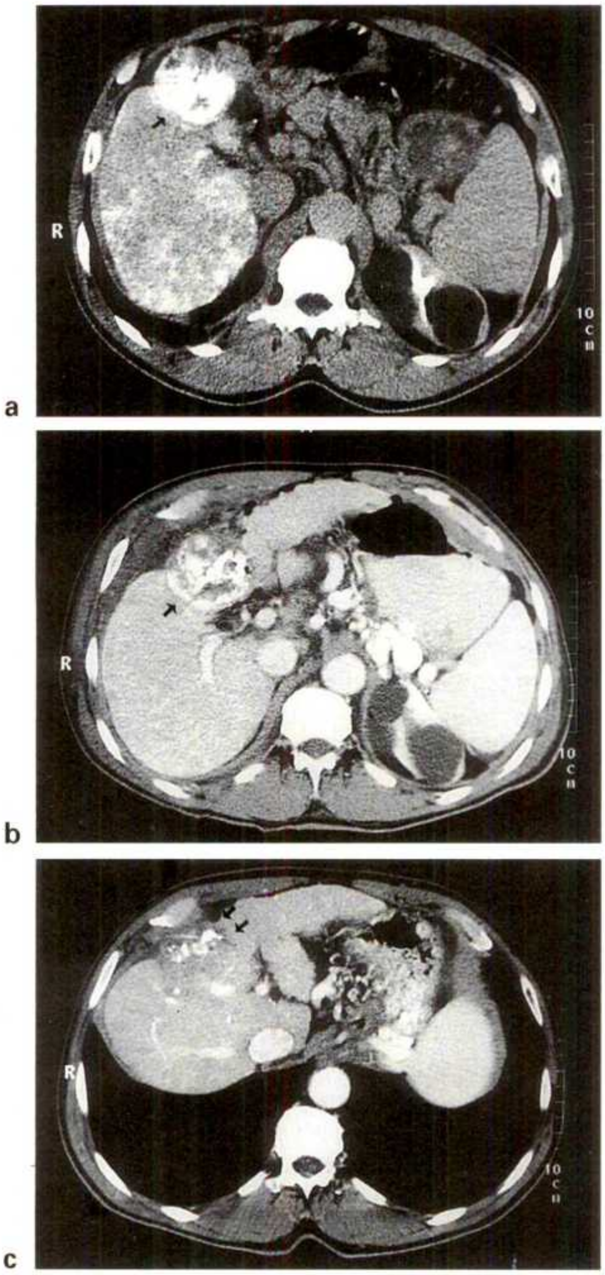

Fig. 3 Contrast-enhanced computed tomogram **a** before, **b** 1 day after and **c** 7 months after laser treatment of a 4·5-cm large hepatocellular carcinoma in the anterior sector of segment four (arrow). Because of cirrhosis, portal flow was negligible during treatment (four fibres with diffusing tips of 5 cm). Through these fibres 12·5 W of neodymium yttrium–aluminium–garnet light per fibre was guided simultaneously over 6 min (4500 J per fibre). In **b** and **c** laser-induced avascularity is seen. In **c** a small enhancing rim (double arrow) indicates incomplete tumour destruction (a second laser treatment was scheduled)

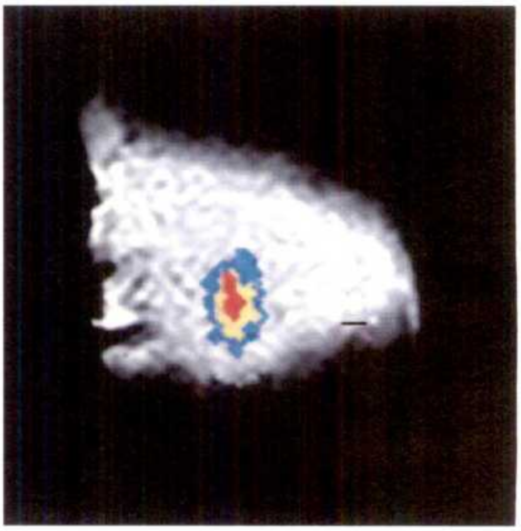

Fig. 4 Magnetic resonance image showing a transverse slice of liver lobe (*ex vivo*) scanned in dynamic series during laser treatment with a single fibre (cylindrical diffusing tip of 2 cm) with 6 W over 6 min. Temperatures were calculated relative to the baseline proton resonance frequency in a reference scan before treatment[90]. Colour overlays, over the baseline morphological image, represent temperature increases compared with those at the start of the experiment (32°C in this particular case): + 8°C (blue), + 18°C (yellow) and + 28°C (red). Temperatures could be determined with an accuracy of ± 3·5 s after 6 min of laser application (95 per cent confidence interval). Correlation between the dimensions of macroscopic coagulation and the largest diameters of the 60°C isotherm was 0·94. Bar indicates 1 cm

resonance variable. The PRF method provides a direct estimate of temperature changes[85], and the feasibility and accuracy of this subtraction technique was demonstrated in 1995[86,87]. In *ex vivo* and *in vitro* models the accuracy of phase-shift mapping was within 4°C[85,88,89] (*Fig. 4*). Respiration-induced artefacts do not result in a decreased accuracy[90]. Currently this technique is under investigation in preclinical models.

For MRI assessment after treatment both T1- and T2-weighted scans have been proposed[91,92]. With sophisticated T1-weighted scans the area of coagulation at the end of treatment could be predicted very accurately. This was investigated in animal models[47,93] and in surgical candidates who underwent resection 2–3 days after MRI-guided laser treatment[49,94] (allowing correlation between MRI and histopathology). In a recent study these encouraging findings were compared with CT, considered as the gold standard, for validation[95]. A good correlation was found between the MRI scan at the end of laser application and the CT scan at 24 h. Currently, space to access the patient is limited in high-field MRI machines; progress in this field and the development of magnetic resonance-compatible equipment promises future high-field MRI with the capacity for intervention from all sides[96,97]

Clinical experience

The cumulative clinical experience is summarized in *Table 2*. The first clinical report came from Hashimoto *et al.*[104] in 1985 who treated patients with liver metastases and HCC at laparotomy. A Nd YAG laser at a low power output of 5 W was used with a relatively long exposure time and a bare-tip laser fibre was employed. From this study it appeared that the technique could be performed without major complications. A drop in tumour marker levels was recorded, but the benefit to patients remained unclear. In later studies the technique was improved using various combinations of power output and exposure times, and adaptation of the fibre tip to avoid carbonization. Hahl *et al.*[105] and Huang *et al.*[106] actually used hyperthermia, instead of direct coagulation, which means that the temperature was held between 41 and 45°C over 10–30 min. A fatal complication was caused by air emboli as a result of interstitial air introduced for cooling of the fibre tip, a method of cooling that has been abandoned ever since.

The percutaneous procedure was introduced by Steger *et al.*[107] and later adapted by Nolsoe *et al.*[99] and Schroder *et al.*[100]. Total eradication of small tumours was described. Failures were noted mostly for lesions larger than 2·3 cm; this threshold for a complete response was also found in a larger series by Vogl *et al.*[77] using single fibre application with a diffusing tip in a percutaneous procedure. In sequel

Table 2 Review of clinical interstitial laser coagulation of hepatic malignancies with emphasis on the treatment response at 6 months

Reference	Year	Group characteristics*	Technique	Approach†
Huang *et al.*[106]	1991	7 HCC (2–4 cm)	Diffusing tip; 2–3 W, 20–30 min	Laparotomy (thermocouple)
Nolsoe *et al.*[99]	1993	16 CRCs (1–4 cm)	Diffusing tip, 4–8 W, 5–45 min	Laparotomy 2 (thermocouple), percutaneous 9 (US)
Amin *et al.*[76]	1993	34 CRCs, 21 secondaries of mixed origin (1–15 cm)	4 × bare tips simultaneously, 2 W, 7 min	Percutaneous (US)
Schroder *et al.*[100]	1994	2 HCC (3–7 cm); 2 breast secondaries, 6 CRCs (0 5–7 cm)	Bare tip; 2–6 W, 8–15 min	Laparotomy (US)
Dowlatshahi *et al.*[101]	1995	45 lesions in 20 patients, HCC and CRCs	Bare tip; 5–10 W, 7 min	Laparotomy (US)
Tranberg *et al.*[102]	1996	3 HCC, 18 CRCs, 1 pancreatic secondary (1–10 cm)	Frosted sapphire tip; 6–10 W, 5 min with complete hepatic inflow occlusion	Laparotomy (US)
Gillams *et al.*[103]	1997	148 secondaries in 55 patients (1–6 cm)	2 × 4 bare tips simultaneously; 2 W per fibre, 7 min	Percutaneous (US and MRI)
Vogl *et al.*[79]	1997	282 CRCs in 99 patients (< 5 cm)	Diffusing tip; 10 W, 10–20 min	Percutaneous (MRI)

a *Values in parentheses are tumour diameters †Monitoring technique is shown in parentheses

Reference	Year	Tumour response at 6 months	Mean (range) no of treatments	Complications
Huang *et al.*[106]	1991	CT. 40% CR, 40% PD	1 1 (1–2)	Mild pain
Nolsoe *et al.*[99]	1993	US· 75% CR (mean 2·4 cm), 25% SD (mean 3 4 cm)	1 only	Mild pain, temperature increase, pleural effusion
Amin *et al.*[76]	1993	CT: 38% CR, 44% SD; failures at > 4 cm in diameter	3·2 (1–8)	Severe pain, subcapsular haematoma, pleural effusion, temperature increase
Schroder *et al.*[100]	1994	CT: 8% CR, 58% SD, 33% PD	1·8 (1–4)	Biloma, vasovagal reaction, shoulder pain
Dowlatshahi *et al.*[101]	1995	CT 68% CR (< 2 5 cm); 0% CR (> 2 5 cm)	1 only	n.s
Tranberg *et al.*[102]	1996	CT· 16% CR, 38% PR, 46% SD/PD	1 only	1 fatal multiple organ failure
Gillams *et al.*[103]	1997	CT 15% CR, 38% PD	2 2 (1–12)	n.s
Vogl *et al*[79]	1997	MRI: cumulative 3-year survival rate 42%	8 (1–36)	Nausea, right subphrenic haemorrhage

b HCC, hepatocellular carcinoma, CRCs, colorectal cancer secondaries, CT, computed tomography; US, ultrasonography, MRI, magnetic resonance imaging, CR, complete response, PD, progressive disease; SD, stable disease, PR, partial response, n s , not stated

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to Steger's study, Amin *et al.*[76] used a method of bare-tip fibre application which required reinsertion and repulling of the fibres to cover the tumour completely. Tranberg *et al.*[102] treated patients at laparotomy with complete hepatic inflow occlusion and from one to four fibres according to tumour size.

Complications

Minor complications such as pain at the fibre insertion site, pleural effusion, local (subcapsular) haematoma, and pain at the shoulder as a result of diaphragmatic irritation, occur in approximately 90, 10, 10 and 15 per cent of patients respectively. The subfebrile temperatures after treatment, reported in several series, may be due to the presence of necrotic tissue in the liver or a sterile peritonitis at the fibre insertion site. That the procedure is fairly easily tolerated is illustrated by the percutaneous protocols in which the patients are usually discharged 24 h after treatment with minimal requirement for analgesia.

Serious complications in the series without flow occlusion are seldom encountered; bilomas or haemorrhages requiring external drainage have not yet been reported. One case of fatal Budd–Chiari syndrome occurred on the day after laser treatment in a patient in London (S. G. Bown, personal communication), emphasizing the need for accurate monitoring of laser-induced effects near vital intrahepatic structures such as the hepatic veins. Tranberg *et al.*[102] reported a death from multiple organ failure due to massive tumour necrosis after laser treatment of an 8-cm lesion. In their series complete occlusion of hepatic flow was applied. The situation may be compared with the 'cryoshock phenomenon' in which multiple organ failure ensued after treating large tumours with cryosurgery[108]. There are no reports of injury to major vascular or biliary structures after ILC close to major portal pedicles with hepatic inflow occlusion, and so such siting is not considered as a contraindication to treatment. In the authors' clinical experience, ILC with portal inflow occlusion of tumours up to 4·5 cm in diameter has always been safe and tolerable.

Outcome

As each study defines its own criteria of selection and evaluation, the outcomes in terms of tumour response and survival are difficult to compare (*Table* 2). In an updated series, Vogl *et al.*[79] evaluated the effect on survival after percutaneous ILC in 99 patients with colorectal metastases of the liver. A 3-year survival rate of 42 per cent with a median survival of 36 months was reported (88 per cent at 1 year). This was at the expense of an average of 2 9 repeated treatments per tumour (range not stated), both for recurrence in treated tumours and for newly diagnosed tumours (not distinguished). In the cumulated London series mean survival was 18 months in 44 patients with an mean number of 2·2 repeated treatments; the 1-year survival rate was 87 per cent[103]. For patients treated at laparotomy, results were less favourable, possibly because of the larger diameters of the treated tumours (up to 10 cm)[102]. Median survival after treatment was 8·5 months and this was mainly influenced by recurrent disease at various extrahepatic sites (in 70 per cent of patients). Recently the first significant series of ILC in patients with HCC was reported; in 12 patients 17 lesions were treated and median survival was 34 months[109]. Currently, in the percutaneous protocols the number of tumours is limited to five and the diameter to 5 cm.

Procedural considerations

ILC can be performed percutaneously under intravenous sedation and analgesia, allowing a short hospital stay with 24-h observation after treatment. On the other hand, general anaesthesia with artificial ventilation results in better respiratory control for respiratory triggered real-time MRI scanning, prevents patient discomfort and movement during treatment, and renders portal inflow occlusion more tolerable. In the authors' experience and as reported by others percutaneous transhepatic catheterization and balloon occlusion of the portal vein can be performed safely by an experienced interventional radiologist[72,73,110]. For lesions high in the hepatic dome, transthoracic and transdiaphragmatic fibre insertion may be necessary. For lesions located in the left hemiliver a subcostal route is feasible, whereas for right-sided tumours insertion in the intercostal space may be considered to avoid vital structures, especially when inserting multiple fibres. An advantage of percutaneous treatment is the feasibility of repeated treatment.

There are also advantages of an open or laparoscopic approach[45,111]. Fibre positioning under direct view may be more reliable, resulting in complete tumour destruction in a single treatment session. Intraperitoneal tumour deposits, making the laser treatment pointless, can be detected at laparotomy or laparoscopy. Needle tract haemorrhage is detected instantly and can be treated under direct vision. The liver can be mobilized allowing access to lesions located posteriorly[112] and, finally, for deep-seated lesions more flexibility is created in choice of the insertion tract. In pigs, laparoscopic ILC has been combined with real-time MRI monitoring in an open interventional magnetic resonance scanner[111]. In this way the precision of positioning under direct view is combined with reliable interstitial monitoring.

Conclusion

ILC is one of the modalities under current investigation for local control of hepatic malignancies. In this review the principles underlying ILC have been discussed. From the results of animal and clinical studies it may be concluded that ILC is safe and feasible using either a laparoscopic approach or percutaneous access. Recent advances are the use of fibres with a cylindrical diffusing light-emitting tip of which the length is adaptable to tumour diameter, water-cooled fibre systems, simultaneous multiple fibre application, and hepatic inflow occlusion during laser treatment. Complete destruction of tumours up to 5 cm in diameter can be realized. In the light of recent developments allowing accurate real-time monitoring with MRI, the authors are optimistic about the role of ILC in the management of hepatic malignancies. Although ILC for hepatic tumours should still be regarded as an experimental treatment[15], it is legitimate to evaluate its impact on the survival of patients with irresectable hepatic tumours. When the accuracy and efficiacy of ILC has been established unequivocally, comparison with surgical resection in controlled clinical trials will be justified.

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Experimental techniques and models in the study of the development and treatment of abdominal aortic aneurysm

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Background: It is still unclear what initiates aneurysmal dilatation and what determines whether or not an aneurysm will continue to expand and rupture. Early detection and operative repair of an abdominal aortic aneurysm (AAA) still remains the only effective means of reducing the high mortality rate associated with the condition. Endovascular techniques are being developed in an attempt to reduce the mortality rate associated with elective repair. A variety of animal models and experimental techniques have been described in the investigation of the pathophysiology of AAA and in the development of improved endovascular surgical and pharmacological therapies. This article discusses these models and techniques, their advantages and some of the problems encountered in extrapolating experimental findings to the human condition.

Methods: This review is based on a search of the Medline database from 1966 to March 1998 using recognized key words and text words. A further search was then conducted on references quoted within selected relevant publications.

Results and conclusion: Treatment of rodent aortas with intraluminal elastase or periaortic calcium chloride creates reproducible aneurysms that have certain similarities to the human pathology; such aneurysms have been favoured in the investigation of the pathophysiology of aneurysm expansion. However, these models lack several of the prominent features of the human lesion, such as atherosclerosis and intraluminal thrombosis. The development of gene knockout mice may lead to a more analogous aneurysm formation, with associated atherosclerosis. Many large animal models have been used in the development of endovascular techniques but, in general, these do not mimic the human pathophysiology and fail to predict medium- and long-term complications.

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Abdominal aortic aneurysm (AAA) rupture is associated with a mortality rate of over 80 per cent and causes 1–2 per cent of all deaths in the UK each year[1]. The natural history of an aneurysm is gradual expansion until rupture occurs and, although there is considerable variability between patients in the rate of expansion and the point of rupture[2], the best method of reducing the associated mortality rate is still to detect AAAs before rupture and repair them electively[3,4]. Endoluminal stent-graft repair has been introduced recently in an attempt to reduce the morbidity and mortality rates associated with elective open aneurysm repair.

The terms 'atherosclerotic aneurysm' and 'non-specific aneurysm' have been used to distinguish the common form of fusiform infrarenal AAA from the rarer hereditary, infective and traumatic lesions. For a long time atherosclerosis has been thought to contribute to aneurysm formation and this association has been supported by population studies[5–7]. However, this type of study cannot differentiate between causal effects and associated risk factors, and it has become clear that atherosclerosis is not the sole cause, not least because many patients who develop occlusive atherosclerotic disease of the aorta never form an aneurysm.

Earlier concepts of aneurysm expansion envisaged a passive degenerative expansion of the aorta but immunohistochemical, biochemical and molecular biological studies on samples of human aneurysms taken at operation have consistently shown large numbers of inflammatory cells in the wall, and increased cytokine and protease activity[8,9]. Matrix metalloproteinases and fibrinolytic enzymes have been found to be more active in aneurysm walls than in samples of occlusive atherosclerosis, and may be at least in part responsible for the destruction of the elastin and collagen structural matrix[10–12]. These observations have led to the concept that an inflammatory process and active proteolysis weaken the structural matrix of the abdominal aortic wall and the high transmural pulse pressure causes aneurysmal dilatation. However, the studies on tissue samples from human aneurysms inevitably deal with a late stage of disease and do not necessarily reflect the conditions that initiated aortic dilatation in the first place.

A better understanding of the mechanisms that initiate and contribute to aortic dilatation may allow effective pharmacological agents to be developed and reduce the need for surgery. These pathophysiological mechanisms and their possible modification by pharmacotherapy have been investigated in a variety of animal models as well as by tissue explant and cell culture techniques, haemodynamic simulations and computer-simulated biomechanical analysis of theoretical wall stresses.

Animal models

An ideal model of a fusiform AAA would include all the pathological features observed in the human condition: atherosclerosis, disruption of the elastic lamellae in the tunica media, adventitial inflammation, increased proteolytic activity in the aortic wall and intraluminal thrombosis. Animal models that reproduce some of these features have been used to investigate factors that contribute to aneurysm expansion and their susceptibility to pharmacological intervention.

Powell[13] classified small animal models into three broad categories: genetically predisposed animal models; medial injury aneurysm models; and haemodynamically induced aneurysm models. Since her review, the advent of gene knockout techniques has shed light on some biochemical aspects of aneurysm expansion and the development of a rat elastase model has allowed the factors that exacerbate continued aneurysm expansion to be studied in more detail. Synthetic aneurysms that resemble the morphology of human aneurysms have proved useful in the development of endovascular repair techniques.

Genetically predisposed animal models of aneurysm

The blotchy mouse spontaneously develops aortic aneurysms and has been used to study aneurysm pathogenesis[14]. This strain of mice possesses a chromosomal mutation that affects copper metabolism and causes abnormal cross-linking of collagen and elastin with consequent weakening of connective tissue[15]. The loss of elastin in the mouse lung and aorta causes emphysema and aneurysms in the aortic arch, descending thoracic aorta and, occasionally, in the abdominal aorta. The elastolysis that occurs is analogous to the association between aneurysms and chronic obstructive airway disease which occurs in humans[16]. The blotchy mouse has been used to investigate the effect of antihypertensive therapy on the development of these hereditary aneurysms[17]. There is, however, no evidence of a similar chromosomal mutation in humans and, although it remains an interesting model, the blotchy mouse appears to have little direct relevance to the pathogenesis of human AAA.

The development of gene knockout techniques, in which mice are bred with a homozygous gene deletion, has provided interesting insight into the development of aneurysm expansion[18]. Mice that lack the gene for apolipoprotein E (Apoe$^{-/-}$) develop atherosclerotic plaques in the aortic wall when fed a high-cholesterol diet. There is subsequent fragmentation of the elastic lamellae in the tunica media, often with ulceration into the media, causing pseudomicroaneurysms to form. These pseudomicroaneurysms are seen in 10–20 per cent of plaques but are contained within the aortic wall by adventitial thickening. Large numbers of macrophages are found around the sites of medial destruction and this is similar to the inflammatory cell infiltrate noted in the media and adventitia of human aneurysms. The same changes are not seen in mice deficient in both apolipoprotein E and urokinase-type plasminogen activator (Apoe$^{-/-}$: Plau$^{-/-}$) suggesting that a reduction in plasmin activity protects against matrix destruction. The Apoe$^{-/-}$ mice reportedly have an aortic diameter which is 50 per cent greater than that of Apoe$^{-/-}$: Plau$^{-/-}$ mice, suggesting that the Apoe$^{-/-}$ mice may have a degree of true aneurysm formation. Human aneurysms are characterized by progressive dilatation of the whole aortic circumference and pseudomicroaneurysms are not a major feature.

The Apoe$^{-/-}$ knockout mouse provides an attractive model because the aneurysms are associated with atherosclerosis but they have not yet been shown to produce progressive aortic dilatation until rupture. The knockout mouse does, however, have potential for determining the effect of fibrinolytic and matrix metalloproteinase enzymes on the destruction of structural proteins in the aortic wall around atherosclerotic plaques.

When segments of aorta are transplanted from guinea-pig to rat, aneurysms develop as part of the ensuing rejection process[19]. This rejection is accompanied by an influx of inflammatory cells into the xenograft, degradation of structural elastin and aneurysm formation. This model has been used as the basis for studies on the effects of plasminogen activator inhibitor (PAI) 1 in limiting the development of aneurysms[20]. When the xenografts were seeded with smooth muscle cells transduced with the rat

PAI-1 gene, the grafts did not become aneurysmal or rupture. The model highlights the potential role for endogenous protease inhibition in limiting aneurysm development, but it is uncertain how analogous xenograft rejection is to human aneurysmal disease.

The importance of the association between atherosclerosis and aneurysm has been further supported by observations in cynomolgus monkeys fed an atherogenic diet. Zarins *et al.*[21] reported that a proportion of these monkeys developed aneurysms after cessation of the high-lipid diet and proposed that aneurysm expansion was initiated by atherosclerotic plaque regression.

Medial and adventitial injury aneurysm models

Several techniques have been developed to reproduce the medial elastic disruption, inflammatory cell infiltration and proteolysis that are found in human aneurysms. These techniques include surgical incision through the tunica media, administration of exogenous proteases or calcium chloride, and activation of endogenous proteases[22–25].

Infusion of elastase via an intra-arterial catheter into an isolated segment of aorta to induce aneurysmal dilatation was first described by Anidjar and Dobrin in 1989[22]. Porcine pancreatic elastase disrupted the medial elastic lamellae and produced a delayed inflammatory infiltration[26]. The activity of endogenous proteases in the aortic wall increased after a latent period[27]. The same changes were produced when activated macrophages were infused into the aorta in the presence of plasmin[22]. Infusion of elastin degradation products alone, in the absence of elastase, also produced some aortic dilatation and adventitial angiogenesis[28].

Hypertension is a major risk factor in human aneurysmal disease[2]; there is interest in the role of antihypertensive therapy in slowing aneurysm expansion and reducing the risk of rupture. Both congenital and renovascular hypertension has been shown to increase the rate of aneurysm expansion and rupture in the Anidjar–Dobrin rat model[29]. β-Adrenergic receptor blockade with propranolol reduces this higher rate of expansion in the congenitally hypertensive rats[30] and has led to speculation on the role of β-blockade in slowing the expansion of small aneurysms unsuitable for surgical repair. Clinical trials of this therapy have been proposed[31].

The presence of inflammation in the aneurysm wall and the increased protease activity, particularly from members of the matrix metalloproteinases class of enzymes[11], provide potential targets for pharmacotherapy. Anti-inflammatory agents and protease inhibitors have been proposed as possible drugs in the treatment of aneurysmal disease. Many of the enzymes that are upregulated in human aneurysm samples are also activated in the Anidjar–Dobrin rat model[27], which has therefore been considered a suitable means of testing these classes of drugs. Tetracycline derivatives including doxycycline, which is a protease inhibitor as well as an antibiotic, reduce the expansion of aneurysms induced in this model[32]. Indomethacin inhibits the expression of metalloproteinases in macrophages and inhibits aneurysm formation[33], and other studies have demonstrated that inhibition of inflammatory cell infiltration by anti-CD18 monoclonal antibody also reduces aneurysm expansion in this model[34].

Other animal experiments have used adventitial damage to initiate aneurysm expansion and so avoid cannulation of the aorta. When elastase is applied to the outer surface of the aorta, the resulting adventitial damage causes some aortic dilatation, lengthening and wall thickening, but not true aneurysm formation[25]. Experiments on the rabbit common carotid artery have shown that aneurysms can be induced by periarterial application of calcium chloride[24], but applying calcium chloride alone to the abdominal aorta of rabbits causes only aortic wall thickening with little dilatation. However, aneurysms develop in the proximal abdominal aorta if the periaortic calcium chloride is combined with a high-cholesterol diet and thioglycollate (an activator of macrophages)[35]. Such aneurysms have an inflammatory cell infiltrate of foamy macrophages and lymphocytes in the adventitia with underlying medial disruption. These changes are analogous to observations in human AAAs but, although hypercholesterolaemia in the rabbit produces lipid accumulation in the aortic wall, it does not usually cause true atherosclerosis[36]. Hyperlipidaemia is also not a recognized risk factor for human aneurysmal disease.

None of the small animal aneurysm models reproduces the complex intraluminal thrombosis that is a prominent feature of almost all human AAAs, often occupying the bulk of the aneurysm sac. Its structure in the human disease is quite unusual (*Figs 1* and *2*) because, while the thrombus on the luminal aspect is a typical fibrin mesh with canaliculi and many inflammatory cells, the deeper juxtamural thrombus is often formed from many layers of organized thrombus characterized by few cells, a fibrinous extracellular matrix, lipid accumulation and occasional calcification[37,38]. Some degree of intraluminal thrombosis may be present in certain small animal models, but when this occurs it seems to consist only of fibrinous deposits on the damaged tunica intima[22] and not the complex organized thrombus characteristic of the human pathology.

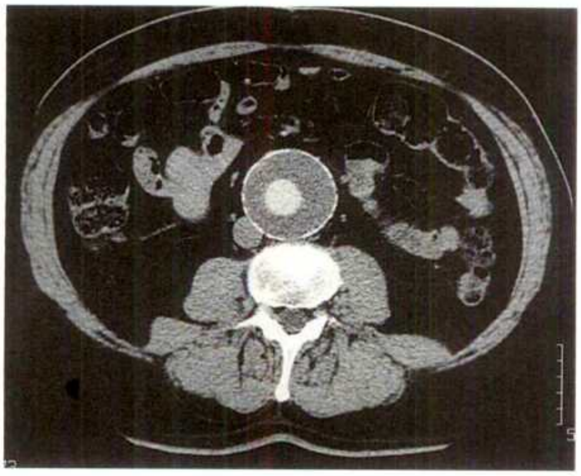

Fig. 1 Computed tomogram of an abdominal aortic aneurysm. The bulk of the aneurysm sac is occupied by intraluminal thrombus, reducing the luminal diameter to near normal

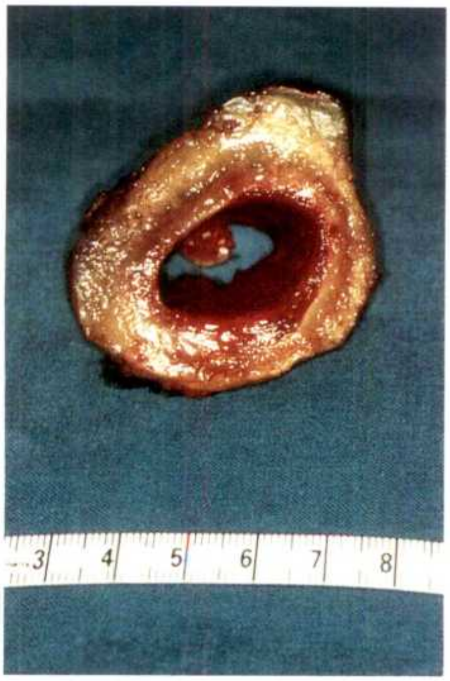

Fig. 2 Transverse section of the intraluminal thrombus from the patient shown in *Fig. 1*. The laminated white thrombus in the deeper layers is comprised mainly of connective tissue and supports the original shape of the thrombus even in the absence of aortic flow

Haemodynamically induced aneurysm models

Arteries dilate in response to alterations in blood flow, and poststenotic dilatation is a common phenomenon[39]. This property has been used to produce a model of AAA by partial ligation of the aorta between the renal arteries[40]. The resultant stenosis produces aortic dilatation and renovascular hypertension. The cotton ligature used in this model induces an inflammatory response which appears to be essential for aneurysmal dilatation to occur.

Poststenotic dilatation has also been used to study changes in protease activity in thoracic aortic aneurysms induced in cynomolgus monkeys. When a stenosis was formed in the mid-thoracic aorta, collagenase activity increased as the aorta dilated over a 3-month period. This observation led to speculation that the increased protease activity in AAAs may be a secondary response to dilatation rather than a primary cause[41]. Although of interest in examining the response of the arterial wall to flow changes, the haemodynamically induced models do not accurately represent the typical human fusiform AAA, in which proximal stenosis is rarely found.

Aneurysm models for endovascular stent-graft development

The endovascular aneurysm exclusion techniques, first reported by Parodi and colleagues in 1991[42], have the potential for lowering mortality and morbidity rates associated with conventional open surgery. There has already been considerable improvement in the design since the early stent-grafts and further developments can be expected. Trials of new designs and insertion methods of endovascular stent-grafts have mostly used canine or porcine models which are similar in shape and dimensions to human AAAs.

Synthetic aneurysm models may be created by suturing an interposition graft or a patch on the anterior wall of the abdominal aorta; the endovascular stent-graft can then be deployed either under the same anaesthetic or as a delayed procedure. A variety of patch materials have been used to construct synthetic aneurysm models. Preformed fusiform Dacron (Du Pont, Stevenage, UK) aneurysms have been used as interposition grafts and have the advantage of consistency in shape and size but they do not preserve the lumbar and mesenteric collateral circulation to the sac[43–46]. Anterior patch techniques do preserve lumbar and mesenteric flow to the aneurysm sac and a variety of autologous grafts have been used as patch material. Anterior patches of jejunum[47] and vein[48–50] form aneurysms that continue to expand and often rupture. Fascial patches may be fashioned from the rectus sheath[51–54] or fascia lata[55] and show less tendency to rupture.

Creating an aneurysm model by the use of endovascular techniques has the advantage of avoiding laparotomy and open aortic surgery. Balloon angioplasty alone, even at very high pressure, does not produce an aneurysm but it can be used to model the deployment of a stent-graft in acute aortic rupture[56]. An aneurysm can, however, be created and maintained if the dilatation is followed by insertion of a balloon-expandable stent[57]. The resulting aneurysm model is lined with an endothelialized metallic stent rather than native aortic wall and it is not clear what effect this has on later stent-graft deployment and fixation.

The experiments on stent-graft deployment in synthetic aneurysms often use angiographic or ultrasonographic examination of the stent-graft as an endpoint, with success judged as complete exclusion of the aneurysm sac from the aortic circulation. However, it is now apparent that the successful deployment of a stent-graft prosthesis and radiological exclusion of an aneurysm does not guarantee continuing success. Continued perfusion of the aneurysm sac by patent lumbar or inferior mesenteric vessels, late endoleak, continued aneurysm expansion and graft migration are some of the late complications that are now recognized[58–62].

The synthetic aneurysms formed in these large animal models do not reproduce many key features of the human disease, such as atherosclerosis, medial destruction, adventitial inflammation and intraluminal thrombosis. Although large animal models are valuable in reducing the early technical complications of human endovascular aneurysm repair, such as maldeployment and unsuccessful radiological exclusion, it is not surprising that there is a failure to predict some late complications. The development of large animal models with the pathophysiological features of the human disease may allow more valid studies of the long-term results of endovascular repair.

One approach to the induction of pathophysiological changes similar to those in humans is to cause aneurysm formation by medial injury in a manner similar that of the Anidjar–Dobrin rat elastase model. Boudghene *et al.*[63] have described the induction of medial elastic disruption and aneurysm formation in dogs by perfusion of an isolated segment of aorta with elastase. Endovascular repair of these aneurysms was undertaken, and successful exclusion and thrombosis of the aneurysm sac was observed. Similar attempts to produce aneurysms in miniature swine with intra-aortic elastase have proved unsuccessful[64]. Although medial elastic disruption resulted, there was no aneurysmal dilatation and complications occurred with occlusive rather than mural thrombosis.

Aortic explants

Experiments on *ex vivo* samples of aneurysmal tissue have proved useful in the study of the structural and biomechanical properties of human atherosclerotic aortas and aneurysms[65]. Dadgar and colleagues[66] examined the effect of buffered collagenase on canine aortic explants and found marked differences in the structural strength of thoracic, suprarenal and infrarenal abdominal aortic segments after digestion of collagen *in vitro*. This study demonstrated that the infrarenal aorta loses more of its tensile strength after disruption of its collagen fibres than the other segments.

A further advantage of *in vitro* research is the ability to apply therapeutic agents directly to aortic tissue without concern for systemic effects, although there is the converse disadvantage of being unable to prove that a similar effect will occur *in vivo*. Explants of porcine aorta have been used to assess the reaction of intact aortic wall to proteolytic stimuli[67]. A segment of porcine thoracic aorta that was incubated in exogenous elastase had increased endogenous protease activity, which was similar to that seen in human operative specimens. This model has been used to examine the effects of protease inhibitors on aortic tissue in the hope of identifying compounds that may slow the progression of the human disease. However, there are major structural differences in the medial thickness, the number of elastic lamellae and vascularity between the thoracic and abdominal segments of porcine aorta, as well as considerable interspecies variation. The direct relevance to the human disease remains open to question.

Cell culture

Cell culture has the advantage of allowing the study of isolated cell lines under controlled conditions. The technique allows detailed study of the biochemical effects of stressors on vascular smooth muscle and other cell types isolated and cultured from aneurysm tissues. Vascular smooth muscle cells cultured from aneurysms produce more of a collagenolytic matrix metalloproteinase, gelatinase A, than those from non-aneurysmal aorta[68]. Several cytokines that have been identified in aneurysms, including interleukin 1β, have been shown to upregulate the expression of the metalloproteinases stromelysin and gelatinase A by aortic cells *in vitro*[69]. The identification of specific inflammatory mediators and proteases in cell culture may eventually lead to the identification of suitable targets for future pharmacological interventions.

Haemodynamic models

Haemodynamic forces clearly play a major role in aortic dilatation and aneurysm formation but many fundamental interactions are still poorly understood. Atherosclerosis, which is such a prominent feature in the walls of AAAs, is known to occur in regions of low shear stress. Some haemodynamic models have been used to study why fusiform aneurysms develop predominantly in the infrarenal aorta and even to question some basic assumptions on the relationship between atherosclerosis and aneurysm formation. One possibility is that the atherosclerosis noted in aneurysms may be a response to the turbulent flow that accompanies localized dilatation[70]. There are considerable difficulties in modelling the complex variations in flow rate, pulse pressure, shear stress and, particularly, compliance of the aortic wall[71]; reservations remain about the direct extrapolation of findings in synthetic aneurysm models to the human disease.

Computer simulations

Advances in computer flow simulations and structural finite element analysis techniques have allowed sophisticated theoretical analysis of the aortic wall tension in aneurysms and its relation to complicating factors, such as atheroma and intraluminal thrombosis.

These techniques suggest that intraluminal thrombus has a significant protective effect in reducing wall tension[72]. They also indicate that the point of maximum stress is at the aneurysm neck. The limitation of computer modelling is the poor quality of a wide range of data concerning variations in aortic wall thickness, bleb formation, adherence to surrounding structures and the mechanical properties of intraluminal thrombus. The mathematical models often entail assumptions regarding steady-state flow, homogeneity of wall structure and compliance that are not necessarily valid in a biological system.

Conclusion

The understanding of the aetiology of AAA has been considerably advanced by the development of appropriate animal models, although none at present adequately reproduces the human lesion. The important aetiological roles of inflammation and proteinases within the arterial wall have been highlighted by these studies, but the role of atherosclerosis and intraluminal thrombosis in aneurysm development has not yet been proven. Human AAAs are almost always accompanied by atherosclerosis but only the Apoe$^{-/-}$ knockout mouse and cynomolgus plaque regression models reproduce true atherosclerosis associated with aortic dilatation. Intraluminal thrombosis is another prominent feature in almost all human AAAs but it too is not reproduced in its complex form in the animal models. There is evidence to suggest that intraluminal thrombus affects aneurysm expansion in the human disease[73], possibly by acting as a reservoir of proteolytic activity or impeding the oxygenation of the aortic wall[74]. The absence of this thrombus in the animal models has limited our current knowledge of the interactions between thrombus and vessel wall.

In vitro techniques may play an important role in assessing interactions at a cellular level and provide an accessible means of studying the proteinase activities and pharmacological sensitivities of individual cell types. Appropriate large animal models are now available for testing endovascular devices, although these must be modified and improved if they are really to replicate the human state.

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Since the beginning of 1998, *Annales de Chirurgie* and *Lyon Chirurgical* have merged into one French language surgical journal Numbers 1, 2 and 3 of 1998 result from this cooperative collaboration A reciprocal digest written by our European Editor, Mr Colin Johnson, is published in the French journal

Laparoscopic surgery

To determine the limits of indications for laparoscopically-assisted vaginal hysterectomy and hysterectomy, Darat *et al.*[1] reported a study on the value of a preoperative scoring system to decide between the conventional and laparoscopic approach. For each patient, a preoperative score was established according to echographic preoperative uterine size (0, less than 10 cm; 1, less than 13 cm; 2, less than 16 cm; 3, 16 cm or more), previous laparotomy (0, nil; 1, one laparotomy; 2, two or more laparotomies), uterine mobility (0–2), pelvic adhesions and endometriosis stage (0, stage I and II; 1, stage III; 2, stage IV of the American Fertility Society). Between January 1991 and December 1996, 662 patients had a hysterectomy: 233 by laparotomy, 252 vaginal hysterectomy and 177 by the laparoscopic method. Some 152 of 177 patients had laparoscopically-assisted vaginal hysterectomy and 25 had laparoconversion. The mean operating time was 163 min. The overall postoperative complication rate was 8 per cent. The hospital stay was 4·8 days for laparoscopically-assisted vaginal hysterectomy compared with 6·2 days for laparoconversion ($P < 0{\cdot}01$). The laparoconversion rate increased according to the score; it was 8 per cent for a score of less than 7 and 80 per cent for a score above 7. The authors concluded that use of this preoperative scoring system may help to identify patients who may benefit from the laparoscopic route and those with a high risk of laparoconversion.

Isolated fallopian tube torsion is infrequent (81 cases reported in the literature). Isolated fallopian tube torsion was revealed by lower quadrant pain, with acute onset and which quickly became worse. Pelvic examination revealed a lateral cul-de-sac pain. Ultrasonography identified a tubal cystic mass with high impedance arterial waveform on colour Doppler sonography. This diagnosis is often difficult. The contribution of laparoscopy is explained by Habib *et al.*[2], with three cases. A 31-year-old suffered from right lower quadrant pain, which worsened during the following 48 h. Laparoscopy revealed a right necrotic fallopian tube with torsion which was resected by laparotomy. A 49-year-old suffered from left lower quadrant pain with progressive onset. Laparoscopy revealed a torsion of the left fallopian tube which was resected. A 76-year-old suffered from left lower quadrant pain for 14 days. Ultrasonography revealed an adnexal mass. Laparotomy revealed a necrotic left fallopian tube torsion which was resected. In case of clinical symptoms suggestive of isolated fallopian tube torsion, the authors' conclusion was that pelvic and endovaginal ultrasonography and laparoscopy are indicated and permit treatment.

To evaluate the results of the laparoscopic surgical treatment of abdominal emergencies, a retrospective study was reported by Henry *et al.*[3]. From May 1991 to September 1995, 200 patients operated by laparoscopy for an acute abdomen were included in this study. The decision to treat the patient by laparoscopy was taken by the surgeon on duty. There were 101 men and 99 women with a mean(s.d.) age of 41(20) (range 11–90) years. The main indications for operation were acute appendicitis (109 patients), acute cholecystitis (52), small bowel obstruction (14) and perforated duodenal ulcer (14). There was no death in hospital. One per cent of patients experienced an operative complication which was treated by laparotomy. Conversion to laparotomy was needed in 13 per cent of cases. The morbidity rate was 9 per cent and reoperation by laparotomy for acute generalized peritonitis secondary to small bowel perforation was necessary in two patients. Mean postoperative hospital stay ranged from 4 to 7 days. The authors conclude that surgical laparoscopic treatment of common abdominal emergencies is safe. The conversion rate is low, as is the complication rate.

Laparoscopic repair *versus* conventional surgical repair (Shouldice and others) of inguinal hernias still constitutes an unresolved problem. Two articles were dedicated to this surgical problem. The aim of the first paper, by Champault *et al.*[4], was to compare the late recurrence rate after a laparoscopic totally preperitoneal approach with that after Shouldice and Stoppa procedures. All patients, from two randomized studies, were reviewed at 1, 6 and 12 months and yearly thereafter. Follow-up was 100 per cent at 1 month, 98 per cent at 6 months, 95 per cent at 1 year, 91 per cent at 2 years, 84 per cent at 3 years, 79 per cent at 4 years and 61 per cent at 5 years (mean 4 years). At 1 year the recurrence rate was 2 per cent in the laparoscopic group, 1 per cent for Shouldice and 0 per cent for the Stoppa procedure (P not significant). At 3 years, the recurrence rate was comparable: 4 per cent for laparoscopy, 5 per cent for Shouldice and 5 per cent for Stoppa respectively (P not significant). At 4 years, the recurrence rate was still not significantly different: 7 *versus* 12 and 10 per cent. In this study, two predictive factors for recurrence in laparoscopic treatment were the size of the mesh and the surgeon's experience. The second paper reported a randomized prospective study comparing the cost of conventional Shouldice repair and transperitoneal laparoscopic repair with polypropylene mesh[5]. Some 64 men were included, between May 1994 and September 1995. Cost evaluation was divided into distinct parts: drugs, disposable surgical materials, medicotechnical procedures, food and employees' costs. In the Shouldice group, mean operating time was 56 min and total cost was 3922 French francs (FF) in the case of unilateral hernia, and 77 min and 4808 FF for bilateral hernia. In the transperitoneal laparoscopic repair group, mean operating time was 89 min and the total cost was 8949 FF (disposable cannulas) or 7136 FF (non-disposable cannulas) in the case of unilateral hernia, compared with 116 min, 9570 FF and 7763 FF for bilateral hernia. Postoperative stay was 4 days after Shouldice repair and 4 days after transperitoneal laparoscopic repair. Return to work was 29 days after transperitoneal laparoscopic repair and 36 days after Shouldice repair (*P* not significant). The authors conclude that laparoscopic hernia repair does not decrease postoperative pain, hospital stay and return to work, but is twice as expensive.

Colonic and rectal surgery

A retrospective analysis of a series of 287 anal canal carcinomas seen during a 15-year period was reported by Gérard *et al.*[6] Twenty-five patients were referred with recurrence. Irradiation was performed after operation in 12 patients and before operation in 23. Palliative treatment was given to 15 patients and simple follow-up in seven. Radiotherapy was given to 205 patients as curative treatment (irradiation alone in 71 and concomitant radiochemotherapy in 134). The overall survival of the group treated by radiotherapy (205 patients) was 72 per cent at 5 years and 61 per cent at 10 years (78 per cent for the group treated by concomitant radiochemotherapy and 60 per cent for the group treated by irradiation alone). The specific survival at 5 and 10 years was 82 and 75 per cent respectively. The authors conclude that radiotherapy should be the standard treatment for anal canal carcinoma. Radiochemotherapy seems to improve results in advanced cases. The best irradiation technique has yet to be defined.

Few data are available in France on the impact of Ostomy Associations on patients with a permanent colostomy. To assess the percentage of patients with permanent colostomy involved in local Ostomy Associations, a survey was made by Goudet *et al.*[7], in a well defined (in 1992) population (Côte d'Or department, 493 931 inhabitants). A minimum number of incident colostomy cases was computed using data from the Digestive Tract Tumor Registry in cases of cancer and using surgical reports from the University Hospital for benign disease. The maximum number of incident cases was computed using results from a survey conducted by the Public Administration (Social Security) during the same period. An interval of prevalent cases was assessed by the number of collecting pouches sold during 1992 in the same area. It was estimated that a colostomy was set up in 37–84 patients; the number of prevalent cases was in the range of 274–410 patients. The corresponding percentage of Ostomy Association members was in the range 8–19 per cent for incident cases and 9–19 per cent for prevalent cases. These values are less than the presumed value of 30 per cent, previously evaluated in a survey conducted among physicians. As the incidence of colostomy continues to decline regularly, the authors conclude that more effective methods must be developed to maintain a constant number of members.

General surgery

Doldi[8] presents an experience of the surgical treatment of morbid obesity. Since 1974, 603 obese patients underwent surgery: 312 jejunoileal bypasses, 70 biliointestinal bypasses, 102 horizontal gastroplasties, 44 silastic ring vertical gastroplasties and 75 adjustable silastic gastric banding procedures. Mean follow-up for these procedures was 16, 6, 11, 4 and 2 years respectively. Weight loss was satisfactory in all cases even though the mean percentage varied in the different procedures: 37 per cent with jejunoileal bypass, 39 per cent with biliointestinal bypass, 31 per cent with horizontal gastroplasty, 5 per cent with silastic ring vertical gastroplasty and 27 per cent with adjustable silastic gastric banding. The most serious complications (severe hepatic failure, oxalic interstitial nephritis, persisting malabsorption) occurred in patients submitted to jejunoileal bypass. The best clinical outcome with the lowest complication rate for an intestinal bypass was obtained with biliointestinal bypass. The most frequent complication observed in patients submitted to gastroplasty was refractory vomiting while the most severe complications were diffuse peritonitis, secondary to gastric perforation, and peripheral neuropathy. The author's experience confirms that surgical treatment of morbid obesity refractory to medical therapy is today a safe and effective treatment. Biliointestinal bypass still has a role in superobese young patients (body mass index over 50) refusing lifelong dietary restriction. The gastric procedures, especially laparoscopic with adjustable silastic gastric banding, seem to be the best option. The excellent outcome of bariatric surgery can be obtained only in specialized centres where various specialists work together.

Intraductal papillary and mucinous tumours are rare. Cuillerier *et al.*[9] retrospectively analysed clinical, surgical and histological features, and outcome of 41 operated patients (29 men, 12 women; mean age 63 years). The commonest presenting manifestation was acute pancreatitis (17 patients). Tumour was located in only one pancreatic segment in 18 patients. Seventeen patients had invasive carcinoma, eight had tumour with severe dysplasia and 16 had lesions with minimal or moderate dysplasia. Only increased age was significantly associated with invasive carcinoma. Eleven of 17 patients with invasive carcinoma had a recurrence after surgery and six died. Among 24 patients with non-invasive tumour, two experienced tumour recurrence without tumour-related death during follow-up (48 months). This study underlines the need for early surgical resection in patients with intraductal papillary and mucinous tumour because of the high frequency of invasive carcinoma and the poor outcome for patients with invasive carcinoma.

Gynaecomastia is the commonest breast lesion in men. Fifty-two operated patients (mean age 24 years) were reviewed by Vasseur *et al.*[10], with a mean follow-up of 2·5 years. Gynaecomastia occurred most frequently during puberty (63 per cent), was bilateral (75 per cent) and idiopathic (65 per cent). The size of the enlargement was evaluated according to Simon's classification[11] based on breast volume and skin redundancy: 18 stage 1, 22 stage 2A, nine stage 2B and three stage 3. Clinical examination and mammography determined the consistency of the gynaecomastia as adipose or firm. Four different surgical managements were used: 32 subcutaneous mastectomies, 12 liposuctions, six liposuctions associated with subcutaneous mastectomy and one total mastectomy. One patient had liposuction on one side and subcutaneous mastectomy on the other. All techniques gave good morphological results. None the less, the authors recommend the combination of liposuction and subcutaneous mastectomy, as this technique presents many advantages: small intraoperative blood loss, good skin cover, short hospital stay and complete histological examination of the material removed.

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Randomized clinical trial of laparoscopic *versus* open inguinal hernia repair

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Background: Several studies have suggested that better results are obtained after laparoscopic repair of inguinal hernia than after conventional operation. This is most obvious for bilateral and recurrent hernias but less accepted for primary unilateral hernias.
Methods: This was a randomized clinical trial comparing transabdominal preperitoneal laparoscopic repair with the Shouldice technique in patients with primary unilateral hernia. Some 138 patients were randomized to laparoscopic hernia repair and 130 to open surgical repair.
Results: The complication rates in the two groups were similar. In the laparoscopic group the patients returned to work more rapidly with a median time of 13 *versus* 18 days ($P < 0{\cdot}005$) and had a shorter period of analgesia intake with a median time of 2·1 *versus* 2·7 days ($P < 0{\cdot}02$). The follow-up was 97·8 per cent complete. At a median of 12 months, four recurrences (2·9 per cent) were detected in the laparoscopic group and three (2·3 per cent) in the open group.
Conclusion: This study shows that in patients with a primary unilateral hernia laparoscopic repair results in less postoperative pain and a quicker recovery than open repair.

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Introduction

Repair of an inguinal hernia is one of the most common surgical procedures. In the past 5 years both laparoscopic and open hernia repair using prosthetic mesh have become increasingly popular. Laparoscopic hernia repair may offer a shorter recovery period owing to less pain, but long-term results regarding complication and recurrence rates still need to be determined[1].

A conventional hernia repair like the Shouldice technique has been proven to give excellent results and currently is probably the best conventional method with which new procedures should be compared[2]. Except for one large multicentre study[3] the series which compare conventional and laparoscopic repair are small and none has stratified between bilateral, recurrent and primary unilateral hernias[3–9].

Most authors agree on the suitability of laparoscopic hernia repair for bilateral and recurrent hernias but there is no agreement whether laparoscopic repair should be universally adopted for a primary unilateral hernia. This paper reports the results of a randomized clinical trial comparing laparoscopic and Shouldice repair in terms of recovery, complications and recurrences in men with a primary unilateral hernia.

Patients and methods

The study was approved by the district ethics committee and all patients gave informed consent. The study took place in the surgical department of a district hospital. Five surgeons participated in the trial; three of the surgeons had performed more than 25, one had performed 15 and one 12 laparoscopic hernia repairs before the start of the trial. The five surgeons were all experienced in the Shouldice repair.

All male patients between 18 and 75 years of age with a primary unilateral hernia referred for elective surgery were eligible for entry into the study. Patients with irreducible hernias and those who were unfit for general anaesthesia were excluded.

All operations were planned as one-day surgery. The patients were randomized to have either a transabdominal preperitoneal (TAPP) laparoscopic repair or open hernia repair with a blind envelope system. The allocation was provided by an independent consultant using computer-generated random numbers.

The laparoscopic technique has been described elsewhere[10]. Under general anaesthesia a 10 × 15-cm polypropylene mesh (Surgipromesh; USSC, Norwalk, Connecticut, USA) was used to overlap the defect widely. It was fixed with staples (EndoUniversal; USSC) to the Cooper's ligament and anteriorly to the abdominal wall.

Conventional repair was performed under general or spinal anaesthesia, and consisted either of a modified Shouldice technique, in which the transversalis fascia was sutured in two layers by a running 2/0 polydioxanone suture, or a sutured narrowing of the internal ring in patients with a small indirect hernia and an intact inguinal floor.

All patients were given a standardized analgesic protocol with tenoxicam 20 mg before surgery and paracetamol after operation for mild and moderate discomfort. For more severe pain they were given buprenorphine according to individual need.

Since differences in advice about when to return to work could affect the validity of this parameter, the patients were equally instructed both verbally and in writing to return to work or their normal activity as soon as they felt able to do so. This recommendation applied to both surgical procedures.

Standardized operative data collection was undertaken by the surgeon. The hernia was classified according to its anatomical presentation as direct or indirect. The operating time was defined as the time from the first incision to placement of the last suture. The recovery period was the time from operation to the time at which the patient had resumed complete normal activities during both employment and leisure time.

Data about operative and postoperative complications were collected. Haematoma was defined as an accumulation of blood which required surgical intervention. Wound abscess was recorded if there was accumulation of pus. Pain in the groin or scrotum which lasted longer than 1 month after operation was recorded as a complication. A recurrence was defined as a clinically detected reducible swelling in the groin.

The patients were examined after 4 weeks, 6–12 months later, and thereafter every year. Because of the placement of the incisions double-blind follow-up was not possible. Information about late complications and the recovery period was obtained. The patients underwent a standard physical examination.

A questionnaire was sent to patients who did not attend the outpatient clinic. They were asked if they had pain/discomfort or a swelling in the groin.

Outcome measures

The aim of the study was to examine the safety and benefits of a laparoscopic method compared with a well evaluated open procedure in a population with primary unilateral hernia. Outcome measures included rate of complications, recurrences, length of recovery period and postoperative pain evaluation.

Statistical analysis

The trial protocol specified a sample size of 254. From the literature it was estimated that the conventional open technique was followed by a recurrence rate of 2·5 per cent[1,11]. With the intention of not missing a worsening of the recurrence rate by introducing a new method, the sample size provided a power of 80 per cent to detect a 10 per cent difference at a 5 per cent level of committing a type I error.

Median (range) values are given for continuous variables. The differences between medians were evaluated using the Mann–Whitney *U* test. Fischer's exact test was used to compare proportions.

Results

Between March 1994 and April 1997, 287 patients entered the study. Nineteen patients were excluded from the trial, of whom 11 had been randomized to the Shouldice operation and eight to laparoscopic surgery. Of these, five did not have a hernia, seven withdrew informed consent, three had an open procedure other than the Shouldice technique (all of whom had an uncomplicated postoperative course), two had no follow-up, in one a laparoscopic procedure was converted to a conventional repair because of adhesions (the patient had an uneventful postoperative course) and one had bilateral hernias.

Some 138 patients underwent laparoscopic surgery and 130 open surgery. In the open surgery group 107 had a

Table 1 Baseline characteristics of patients in the laparoscopic and open surgical repair groups

	Laparoscopic (n = 138)	Open (n = 130)
Age (years)*	48 (18–75)	49 (20–72)
Weight (kg)*	77 (60–110)	78 (56–103)
General anaesthesia	138	52
Spinal anaesthesia	0	78
Indirect hernia	94	82
Direct hernia	44	48

*Values are median (range)

Table 2 Results related to the operation and postoperative recovery

	Laparoscopic (*n* = 138)	Open (*n* = 130)	*P*†
Operating time (min)*	77 (30–200)	45 (20–80)	< 0·001
Hospital stay (days)*	1 (1–3)	1 (1–12)	0·30
Use of postoperative analgesia (days)*	2·1 (0–40)	2·7 (0–21)	< 0·02
Patients who did not require analgesia	69	45	< 0·02
Time to resume complete normal activities (days)*	13 (1–56)	18 (3–55)	< 0·005

*Values are median (range) †Fisher's exact test

Table 3 Postoperative complications

	Laparoscopic (*n* = 138)	Open (*n* = 130)	*P**
Wound abscess	2	0	0·54
Symptomatic haematoma	0	2	0·48
Pain continued > 1 month	10	12	0·74
Testis atrophy	0	1	0·97
Infection of the mesh	1	–	

* Fisher's exact test

Table 4 Postoperative follow-up and recurrence

	Laparoscopic (*n* = 138)	Open (*n* = 130)
Clinical follow-up		
After 1 month	138	130
After 8–24 months	124	119
Follow-up by questionnaire	11	8
Follow-up (months)*	12 (8–17)	12 (8–23)
Recurrence†	4 (2·9)	3 (2·3)

*Values are median (range), †values in parentheses are percentages

Ninety-five per cent confidence limits of the difference between the two recurrence rates 0·6 ± 3·8 per cent

Shouldice operation and 23 had a sutured narrowing of the internal ring. Baseline data for the two groups are shown in *Table 1*.

The median duration of surgery was significantly shorter for the conventional repair. Patients in the laparoscopic group had a shorter period of analgesia use. Some 50·0 per cent of patients (69 of 138) in the laparoscopic group did not use analgesia at all compared with 34·6 per cent (45 of 130) in the open group. Patients who underwent a laparoscopic repair were able to resume normal activities sooner than those in the open surgery group. Nearly all patients (262 of 268) were discharged from the hospital less than 24 h after surgery. Five were discharged between 24 and 48 h and one patient was admitted for 12 days because of severe testicular pain. He was later found to have an atrophic testis. The six patients were equally distributed between open and laparoscopic repair (*Table 2*.)

There was a similar rate of complications between the two groups (*Table 3*). One patient in the laparoscopic group had a mesh infection at 6 months, which required removal of the mesh. Patients who had pain in the groin for more than 1 month were all pain-free 6–12 months later.

There was complete clinical follow-up after 1 month (*Table 4*). Two hundred and forty-three patients (90·7 per cent) were seen in the outpatient clinic from 8 to 24 months after operation. Of the 25 patients who did not attend 19 (7·1 per cent) answered a questionnaire. Of the six patients who were lost to follow-up, one died from a brain tumour, three had moved out of the country and two did not want further examination. Median follow-up was 12 (range 8–17) months for the TAPP repair group and 12 (range 8–23) months for the open repair group.

Seven recurrences were detected clinically, four (2·9 per cent) in the laparoscopic group and three (2·3 per cent) in the open repair group. The 95 per cent confidence limits of the difference between the two rates of recurrence are 0·6 ± 3·8 per cent.

Discussion

This study is the largest published trial from a single institution and it contains uniform data on primary single hernias in men.

It has been reported from other trials[3–5,9] that laparoscopic repair offers patients a quicker recovery, but all types of hernia were included in these trials. The fact that open operation for bilateral and recurrent hernias is more traumatic than that for an uncomplicated hernia makes it uncertain how valid this overall difference in recovery is for the latter type of hernia. This trial confirms that patients with uncomplicated hernias recover more rapidly after laparoscopic surgery than after open repair, as assessed by the analgesia intake and the recovery period.

The trial shows no difference in the rate of complications which is similar to other reports[3,5,12]. Infection of the polypropylene mesh is a rare complication; it has been estimated to occur at a rate of less than 0·5 per cent and has been reported after both open and laparoscopic surgery[13].

Clinical examination during follow-up is indispensable to identify true rates of recurrence. In this trial, patient follow-up was nearly complete. After 1 year there was no difference in recurrence rates and the 95 per cent confidence limit for the difference was so low as to be without clinical importance. Only one large multicentre trial[3] has shown an increasing difference after the first year, with fewer recurrences in the laparoscopic group, but the laparoscopic procedure was compared with a suboptimal open surgery group which included many different types of open operation.

In patients with a primary unilateral hernia laparoscopic repair results in less postoperative pain and a quicker recovery than open repair, but long-term follow-up is warranted to determine recurrence rates.

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Survey of antibiotic prophylaxis in acute pancreatitis in the UK and Ireland

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Background: Current surgical practice with regards to antibiotic prophylaxis in acute pancreatitis in the UK and Ireland was overviewed.
Methods: The 1103 members of the Association of Surgeons of Great Britain and Ireland were surveyed by postal questionnaire. A total of 528 replies were received (48 per cent). Following exclusion of surgeons not treating patients with acute pancreatitis, analysis was carried out on 429 replies.
Results: Respondents treated a median of 12 (interquartile range (i.q.r.) 10–20) patients per year with acute pancreatitis. Prophylactic antibiotic therapy was used by 88 per cent of responding surgeons, of whom 24 per cent used it in all cases. For surgeons professing selective use of antibiotics, the most common indication for use was in patients with prognostically severe disease. A cephalosporin was prescribed in 72 per cent of patients; cefuroxime was the single most common antibiotic. Combination therapy with metronidazole was used in 48 per cent of attacks. The median duration of antibiotic therapy was 5 (i.q.r. 5–7) days. An adverse drug reaction attributable to the use of prophylactic antibiotics was reported by 11 per cent of respondents.
Conclusion: This study has established that a significant body of clinicians charged with the responsibility of treating acute pancreatitis use antibiotic prophylaxis in the initial treatment of patients with predicted severe disease.

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Introduction

Recent evidence suggests a benefit from the use of prophylactic antibiotics in prognostically severe acute pancreatitis[1]. However, the results are inconsistent giving rise to the potential for disparate clinical practice. The aim of this study was to establish an overview of current surgical practice with regard to antibiotic prophylaxis in patients with acute pancreatitis in the UK and Ireland.

Materials and methods

A postal questionnaire was sent to the 1103 members of the Association of Surgeons of Great Britain and Ireland (ASGBI) during November 1997. The questionnaire sought information relating to the indications for, the choice of agent and the duration of antibiotic prophylaxis in acute pancreatitis. A total of 528 replies were received (48 per cent). Eighteen of the respondents had retired, while 14 questionnaires were returned unopened. A further 67 replies were removed from analysis because the respondents either did not treat patients with acute pancreatitis ($n = 40$) or did not indicate the number of patients treated ($n = 27$). Analysis was carried out on the results of 429 postal questionnaires (39 per cent). Surgeons were asked to state whether they had an interest in hepatopancreatobiliary (HPB) surgery, but were not asked to define the level of this interest.

Results

The median number of patients treated per annum by respondents was 12 (interquartile range (i.q.r.) 10–20). Surgeons with a declared interest in HPB surgery treated more than those who did not (20 (i.q.r. 12–28) *versus* 10 (8–15)).

Of the respondents, 411 (96 per cent) of 429 categorized patients at admission into prognostically mild or severe categories with 341 (83 per cent) of 411 using an objective prognostic scoring system. Clinicians categorized disease severity using the following systems: 284 (69 per cent) of 411 used clinical impression, 197 (48 per cent) used the Glasgow/Imrie scoring system, 139 (34 per cent) used Ranson's criteria, 45 (11 per cent) used the Acute Physiology And Chronic Health Evaluation II scoring system, 79 (19 per cent) used serum C-reactive protein concentrations, 47 (11 per cent) use computed tomography-based systems and 12 (3 per cent) used another system. Of the 284 clinicians who reported using subjective clinical impression, 217 (76 per cent) combined this with an objective scoring system.

Prophylactic antibiotic therapy in acute pancreatitis was used by 375 (88 per cent) of 429 respondents. Of those using antibiotics, 90 (24 per cent) of 373 surgeons used them in all cases (two respondents provided no details regarding their indications for use of antibiotic prophylaxis). For the group professing selective use of antibiotic prophylaxis the indication for use was: prognostically severe disease, 229 (81 per cent) of 283; radiological evidence of pancreatic necrosis, 185 (65 per cent); jaundice, 138 (49 per cent); and organ dysfunction, 95 (34 per cent). *Table 1* indicates antibiotics used. A cephalosporin was used in 72 per cent of cases; cefuroxime was the most commonly used. Combination therapy utilizing metronidazole was used in 48 per cent of cases.

For 47 (14 per cent) of 346 respondents the duration of prophylaxis was dependent on clinical course. For respondents stating a duration, antibiotic therapy was continued for a median of 5 (i.q.r. 5–7) days.

Prophylactic antibiotic therapy in acute pancreatitis was governed by hospital policy for 46 (11 per cent) of 426 respondents.

Table 1 Choice of antibiotic for prophylactic therapy in patients presenting with acute pancreatitis

Antibiotic	No of respondents (*n* = 373)
Aminopenicillin	5 (1)
Co-amoxiclav	49 (13)
'Broad spectrum'	3 (1)
Cephalosporin (unspecified)	53 (14)
Cefotaxime	33 (9)
Ceftazidime	1 (0)
Ceftriaxone	3 (1)
Cefuroxime	171 (46)
Cephradine	7 (2)
Ciprofloxacin	7 (2)
Flucloxacillin	1 (0)
Gentamicin	2 (1)
Imipenem	13 (3)
Meropenem	5 (1)
Piperacillin	1 (0)
Piperacillin/tazobactam	5 (1)
Vancomycin	1 (0)

Values in parentheses are percentages

A total of 54 adverse drug reactions secondary to antibiotic prophylaxis were reported by 46 (11 per cent) of 429 respondents. These consisted of 40 cases of fungal infection, six of pseudomembranous colitis, five of methicillin-resistant *Staphylococcus aureus*, two of bacterial overgrowth and one false-negative bacteriological culture on fine-needle aspiration cytology of pancreatic necrosis.

Discussion

When interpreting the results of this study the potential for bias in a questionnaire survey should be borne in mind. Although the response to the questionnaire was encouraging, the return of 528 of 1103 questionnaires represents only 48 per cent of the register of the ASGBI membership list.

The findings of this study suggest that the prescription of prophylactic antibiotics in acute pancreatitis has become widespread, with 88 per cent of respondents prescribing prophylactic antibiotics in acute pancreatitis. Encouragingly, the most common indications for use were those validated by randomized controlled clinical trials, namely prognostically severe acute pancreatititis and pancreatic necrosis[2,3]. In line with current UK guidelines[4] the majority of respondents (76 per cent) use objective prognostic systems in addition to clinical assessment to identify those with severe disease. However, a significant minority of surgeons (24 per cent of respondents) prescribe antibiotics to all patients with acute pancreatitis. This non-selective policy leads to treatment of patients with mild disease in whom prophylactic antibiotic therapy is unlikely to be beneficial. Encouragingly, 50 per cent of those prescribing antibiotics use one that has been demonstrated to be beneficial in severe acute pancreatitis[1].

Finally, with 11 per cent of respondents reporting a serious adverse drug reaction there needs to be awareness that antibiotic prophylaxis in acute pancreatitis is not without risk.

In conclusion, the findings of this study suggest that the recommendations made in the current UK guidelines for treatment of acute pancreatitis[4] are being applied and that antibiotic prophylaxis presently forms part of the initial treatment for patients with prognostically severe acute pancreatitis in Britain and Ireland.

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Original article

Dietary intake after pancreatectomy

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Background: Nutritional intake after pancreatectomy may be impaired. The extent of the problem and the effect on intake of specific nutrients is unknown.

Methods: A 1-week weighed dietary food intake (using digital scales and a food diary) was studied in 15 patients, a median of 4 (range 1–30) months after pancreatectomy. Results were expressed as a percentage of estimated average requirement (EAR), reference nutrient intake (RNI) or lower RNI (LRNI) values.

Results: The median energy intake was 1914 (range 1154–2804) kcal/day, representing a median of 88 (56–154) per cent of EAR. Fat intake was low (72 (60–123) g/day); protein intake was adequate (139 (99–219) per cent of RNI). Deficiencies were observed in the intake of vitamin D (17 (6–56) per cent of LRNI) and, in some patients, selenium (107 (19–203) per cent of LRNI).

Conclusion: Nutritional intake in the months after pancreatectomy could be improved by increasing fat intake (with enzyme supplements as appropriate). This 7-day study also suggests that these patients may require vitamin D and possibly selenium supplementation.

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Introduction

After major pancreatic surgery many patients are unable to return to their usual premorbid diet. The reasons for this include reduced gastric volume after partial gastrectomy, reduced tolerance of fat, postoperative fatigue and anorexia. Reduced intake of nutrients may impede postoperative recovery. There is little published information on dietary intake after pancreatic surgery. This study determined dietary intake in patients who had undergone pancreatectomy by recording overall dietary intake and the intake of energy, nutrients and micronutrients. These observations were compared with recommended intakes in order to identify possible deficiencies.

Patients and methods

Patients were identified in a follow-up clinic devoted to patients with pancreatic disease. After operation patients were discharged with standard written dietary advice and followed personally by the senior author (C.D.J). Medication was prescribed on the basis of symptoms and results of pancreatic function tests. Patients were approached in the clinic by a research dietitian and asked to participate.

Fifteen patients of median age 61 (range 40–76) years were recruited to the study a median of 4 (range 1–30) months after operation; all but three were recruited within 5 months. Patients were interviewed by the dietitian and instructed in the use of digital scales (Soehnle 8020 scales; Paper, Chemical and General, Scunthorpe, UK) and a food diary, and were asked not to change dietary habits. No dietary advice was given by the dietitian. Each patient then recorded weighed food intake for 7 days. The patient returned the scales and food diary to the dietitian, who verified the entries in an interview with the patient. The contents of the food diaries were entered into a computer program for nutritional analysis using COMP-EAT 4.0 (Carlson Bengston Consultants, London, UK). The output from this program was entered into SPSS (SPSS, Chicago, Illinois, USA) for statistical analysis. Median values were calculated for recorded intake of energy, fat, carbohydrate, protein and a range of vitamins and minerals, including vitamins A, D, E, C and folate and the minerals magnesium, zinc, iron and selenium. Intake of energy was expressed as a percentage of estimated average requirement (EAR)[1], with intake of fat and carbohydrate expressed as energy contributions of the total. Protein intake was expressed as a percentage of the reference nutrient intake (RNI) value, defined as the amount of the nutrient that is sufficient, or more than sufficient, for about 97 per cent of people in a group[1]. Vitamin intake was expressed as a percentage of the lower reference nutrient intake (LRNI) value, defined as the amount of nutrient that is sufficient only for the few people in a group who have low needs[1].

All patients had undergone resection of the pancreatic head and duodenum with anastomosis of the body of the pancreas to the posterior wall of the stomach as an end-to-side pancreaticogastrostomy[2]. Eleven patients had a distal gastrectomy and four a pylorus-preserving pancreatectomy. One patient had chronic pancreatitis and two had duodenal carcinoma. The remainder had pancreatic ($n = 9$) or periampullary ($n = 3$) carcinoma. Six patients underwent radiotherapy to the pancreatic head region after resection, 2–4 months before the study. Four patients admitted to significant preoperative alcohol consumption (more than 80 g per day). The patient with chronic pancreatitis had a low alcohol consumption and her pancreatitis was thought to be idiopathic.

Results

All patients except one weighed less than before operation (median reduction 8·3 (range 0–20) kg).

Two patients showed evidence of malnutrition, as determined by a body mass index[3] (BMI = body-weight (kg) / height (m^2)) of less than 19. Median weight was 63 (range 35–101) kg. Median BMI was 21 (range 14–40); all but one patient had a BMI of 27 or less. Three patients were taking pancreatic enzyme supplements at the time of the study and no patient had clinical evidence of malabsorption. One patient who required oral hypoglycaemic drugs before operation required insulin after operation; one other patient became diabetic after operation (oral medication).

Energy intake ranged from 1154 to 2804 kcal. The median percentage of EAR for energy intake was 88 per cent and one-third of patients had an energy intake of less than 75 per cent of the EAR value (*Table 1*). The contributions of fat, protein and carbohydrate to the dietary intake and percentage energy contribution are shown in *Table 1*. The intake of protein expressed as a percentage of RNI was greater than 100 per cent in all but one patient (who had a value of 99 per cent).

The dietary intake of vitamins A, D, E, C and folate are shown in *Table 2*. Vitamin A and E intake met the lower LRNI value. Intake of vitamin D was grossly insufficient in all patients, but they all met the LRNI value for vitamin C and folate.

Table 3 shows the percentage of the LRNI value for various minerals. The mean intake of magnesium and

Table 1 Median energy, fat, carbohydrate and protein intake, observed values and percentage of estimated average requirement, energy intake or reference nutrient intake in 15 patients

	Median (range)
Energy intake (kcal)	1914 (1154–2804)
Energy as a percentage of EAR	88 (56–154)
Fat intake (g/day)	72 (60–123)
Fat as a percentage of energy intake	37 (28–47)
Carbohydrate intake (g/day)	234 (105–331)
Carbohydrate as a percentage of energy intake	44 (31–53)
Protein intake (g/day)	74 (48–117)
Percentage of RNI protein	139 (99–219)

EAR, estimated average requirement, RNI, reference nutrient intake

Table 3 Daily intake of minerals and trace elements observed values and percentage of lower reference nutrient intake value

Mineral or trace element	Intake	Percentage of LRNI
Magnesium (mg)	218 (143–395)	136 (75–208)
Zinc (mg)	9 (6·1–13·5)	179 (111–245)
Iron (mg)	12 (3·9–23·0)	251 (83–490)
Selenium (μg)	43 (7·7–81)	107 (19–203)
Calcium (mg)	983 (581–1451)	245 (145–363)

LRNI, lower reference nutrient intake

Table 2 Median intake of vitamins A, D, E, C and folate. observed values and percentage of lower reference nutrient intake value in 15 patients

Vitamin	Vitamin intake	Percentage of LRNI
A (μg) ($n = 15$)	848 (504–5760)	272 (201–994)
D (μg) ($n = 13$)*	2·0 (0·6–7·1)	17 (6–56)
E (mg) ($n = 15$)	4·6 (2·0–6·5)	152 (102–237)
C (mg) ($n = 13$)*	57 (8–134)	453 (180–878)
Folate (μg) ($n = 15$)*	237 (107–326)	237 (107–326)

Values are median (range). *Missing values unobtainable from computer program LRNI, lower reference nutrient intake

Table 4 Monounsaturated fatty acids, polyunsaturated fatty acids and saturated fatty acids as a percentage of total energy intake

	Percentage of energy intake		Recommended percentage composition of the diet[5]
	Patients*	UK average†	
MUFAs	11·3 (7·3–14·8)	11·6	12
PUFAs	3·1 (1·6–6·0)	6·0	6
SFAs	17·0 (10·8–24·2)	16	10
Total fat	37 (28–47)	35	35

*Values are median (range), †excludes alcohol MUFA, monounsaturated fatty acid, PUFA, polyunsaturated fatty acid, SFA, saturated fatty acid iron, and the intake of zinc and calcium in all patients was greater than 100 per cent of the LRNI value. There was a wide range for selenium intake (median 107 (range 19–203) per cent).

Table 4 shows the relative contributions of unsaturated and saturated fats to energy intake.

There were no obvious differences in any of the reported values in the small subgroup of patients who underwent pylorus-preserving pancreatectomy.

Discussion

These patients, who had recently undergone major pancreatic surgery, had surprisingly normal dietary intakes, although a significant minority had an energy intake lower than 75 per cent of EAR. Fat intake was relatively low compared with normal UK intake[4]. Some deficits in vitamin and mineral intake were also discovered.

The weighed dietary record is the most accurate method available for recording food intake but it has limitations. For energy, a 7-day record is sufficient for an accuracy of ±10 per cent; for vitamins and minerals a longer period of 14 days is recommended[5]. However, the present data indicate that these patients are likely to have a deficient intake of vitamin D, and in some cases of selenium.

Vitamin D intake was low, but this vitamin can also be synthesized in the skin on exposure to sunlight. The mean dietary intake of vitamin D was about two-thirds of the recorded intake of adults in the UK[1], but further study with measurement of blood levels of vitamin D and selenium is required to confirm that these observations represent a true nutritional deficiency.

While some authors have recorded evidence of malnutrition (albumin levels, BMI, body-weight) after pancreatectomy, little attention has been paid to nutritional intake[6–9]. A study of nutritional status after pancreaticojejunostomy paid scant attention to intake[10], focusing more on the effects of enzyme supplementation on absorption. In patients with irresectable pancreatic cancer, nutritional status was assessed by body-weight and BMI, and anthropometry, with no mention of dietary intake[11].

Pancreatectomy may affect appetite, and other influences such as fat intolerance, steatorrhoea and inappropriate dietary advice may affect nutrient intake adversely. With normal intake, absorption of fat and micronutrients can be achieved with appropriate enzyme supplements[12]. The value of the present study lies in the demonstration of suggested shortfalls in intakes of energy, fat, vitamin D and selenium after pancreatectomy. The use of weighed food intakes uncovered these nutritional deficits, despite apparently normal body-weight (BMI 20–26) in almost all subjects.

The reduced energy intake could be attributed to overall dietary deficiency resulting from anorexia, as a non-specific effect of recovery from surgery, but patient recruitment was delayed until patients had spontaneously expressed the observation that they were beginning to feel better and their appetite was returning. It was a clinical impression that patients were consciously restricting fat intake because of inappropriate dietary advice received from non-specialists or because of symptomatic steatorrhoea on an increased fat intake. The number of patients receiving pancreatic enzyme supplements was relatively small ($n = 3$) and it would probably be beneficial for some patients to increase fat intake (with the addition of pancreatic enzyme supplements if necessary) to increase energy intake, which would help to overcome the adverse nutritional effects of the operation and preceding illness. Increased fat intake should also help to increase vitamin D intake, which was grossly insufficient in all patients.

It was encouraging that relatively few nutritional deficits were detected by the analysis of micronutrient intake. Consideration should be given to supplementation with selenium and possibly vitamin D. Selenium deficiency may be a possible causative agent in chronic pancreatitis[13], and selenium was included in a mix of beneficial antioxidants in the treatment of chronic pancreatitis[14]. A relative lack of selenium after pancreatic surgery could predispose to pancreatic fibrosis, particularly if stricturing occurs at the anastomosis[15,16]. It is of interest that four patients with selenium deficiency have been reported recently amongst those requiring nutritional support after major upper gastrointestinal surgery including pancreatectomy[17].

Attention to nutritional intake after pancreatic resection is important. Most patients with pancreatic cancer will survive for less than 2 years after resection[18,19] and the quality of remaining survival should be a primary concern. Inadequate dietary intake could be a factor contributing to impaired quality of life, and this study shows that fat and energy intake is often suboptimal. Vitamin D and selenium supplements may be required if dietary and/or lifestyle adjustments cannot rectify low levels of intake.

Further studies are necessary to determine long-term nutritional intake in patients after pancreatic surgery, whether aggressive pancreatic enzyme substitution can improve dietary intake, and whether the deficits in intake of micronutrients lead to deficiencies in plasma levels.

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Liver metastases after curative resection in patients with distal bile duct cancer

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Background: Curative resection cannot ensure long-term survival for patients with distal bile duct cancer. The aim of this study was to determine the most frequent mode of recurrence after curative resection and to analyse its risk factors.
Methods: Clinical details for 64 consecutive patients with distal bile duct cancer who underwent surgical resection between 1980 and 1997 were reviewed. Modes of recurrence and clinicopathological findings were analysed based on the residual tumour (R) classification.
Results: The overall actuarial 5-year survival rate was 32 per cent. Of 42 patients undergoing R_0 resection 10 were alive at 5 years, of 17 having R_1 resection one was alive at 5 years, and none of the five patients having R_2 resection survived for 5 years (R_0 *versus* R_1, $P = 0.02$). In the R_0 group, the incidence of liver recurrence (14 of 42 patients) was similar to that in the R_1 resection group (six of 17), although there were fewer lymph node and peritoneal recurrences than in patients who had R_1 resection ($P < 0.05$). The high-risk factor for liver metastasis was microscopic vascular involvement. Important factors for survival were lymph node metastasis, microscopic vascular involvement and age. In addition, microscopic vascular involvement was the only independent factor for survival in the R_0 group.
Conclusion: R_0 resection provided significant survival benefit but had no effect on liver recurrence. Therefore, new agents or strategies to prevent liver metastasis are necessary for improvement of survival.

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Introduction

Distal bile duct cancer is a more favourable subtype of periampullary cancer than pancreatic cancer[1,2], and surgical resection is the standard treatment because of the low mortality rate (less than 5 per cent) associated with pancreatic resection[2–7]. Curative resection, the complete surgical removal of the bile duct tumour, offers the only chance of cure, but long-term survival for patients with distal bile duct cancer is limited in comparison with that in patients with ampullary cancer[8]. Five-year survival in patients with lymph node involvement is rare[1,8,9], even though lymph node dissection has been performed aggressively in the past decade[10]. In addition, curative resection cannot ensure long-term survival, even for patients without lymph node involvement[1,11].

Tumour status after surgical resection is defined according to the residual tumour (R) classification of the Union Internacional Contra la Cancrum[12], and margin-free resection has been generally considered as curative resection. This definition of R classification can be used effectively to analyse factors influencing survival and modes of recurrence after surgery for patients with distal bile duct cancer.

The aim of this study was to determine the most frequent mode of recurrence after curative resection and to analyse its relation to unfavourable prognostic factors in patients with distal bile duct cancer.

Patients and methods

The tumour registry and hospital records of 70 consecutive patients with a pathological diagnosis of distal bile duct cancer treated at Kagoshima University Hospital between 1980 and 1997 were reviewed retrospectively. Sixty-four patients underwent surgical resection, a resectability rate of 91 per cent. Of the 64 patients, 42 were men and the mean age was 67·4 (range 39–83) years. All the patients were Asian. Histological examination was performed by experienced pathologists emphasizing the following parameters: determination of the epithelium of origin of the carcinoma, lymph node metastasis, differentiation grade, pancreatic invasion, duodenal invasion, microscopic lymphatic involvement, microscopic vascular involvement, microscopic perineural invasion and resection margin involvement.

The main tumour was located in the lower third of the common bile duct in 31 patients (48 per cent), in the lower and middle third in 29 (45 per cent) and in the middle third in four (6 per cent). Patients with intrahepatic or perihilar duct cancer were excluded from the study[13]. Standard pancreaticoduodenectomy with an attempt at regional lymph node dissection and hemigastrectomy was performed in 33 of the 64 patients. Pylorus-preserving pancreaticoduodenectomy (PPPD) was undertaken in 25 patients. In these patients, the pancreas was transected at the left of the portal vein, the duodenum was dissected and divided about 2–3 cm from the pylorus, regional lymph node dissection was performed, and frozen sections of the duodenal transection margin were examined. PPPD was converted to a standard pancreaticoduodenectomy if the duodenal margin was positive. Lymphadenectomy during PPPD did not include the lymph nodes along the lesser and greater gastric curvatures. Pyloric lymph nodes were examined by frozen section. Total pancreatectomy was performed in only one patient, and resection of the extrahepatic bile duct was carried out in five patients. The operation was classified according to the R classification[12]: R_0 resection, no residual tumour; R_1, microscopic residual tumour; and R_2, macroscopic residual tumour. Histopathological tumour staging for all patients was carried out using the pathological tumour node metastasis (pTNM) postsurgical classification for extrahepatic bile ducts[12].

Before operation no patient was given any chemotherapy or radiotherapy, and perioperative adjuvant therapy was not performed. After operation, patients who agreed to postoperative chemotherapy were given a daily oral dose of 300 mg 5-fluorouracil. This adjuvant chemotherapy was started within 30 days after surgery and the treatment period was 1 year unless symptoms worsened or serious side-effects occurred.

Long-term outcome was determined by review of outpatient records as well as direct patient contact. All patients were available for follow-up. The median follow-up was 34 (range 15–180) months. Regular medical checks at 3-month intervals were made to detect recurrent tumours in the liver, lung and para-aortic lymph nodes using computed tomography, ultrasonography and magnetic resonance imaging. The determination of tumour markers as an auxiliary examination, such as estimation of carcinoembryonic antigen and CA19–9 levels, was undertaken.

The initial recurrent tumour detected with these methods was registered as the mode of recurrence. When mass lesions were found in the liver, angiography via the proper hepatic artery was performed to confirm the metastatic lesions, if necessary. The initial type of recurrent tumour was reconfirmed carefully by several examinations. When different sites of recurrence were found in the same patient at the same time, they were defined as two modes of initial recurrence. Modes of recurrence were defined as follows: liver recurrence – the appearance of single or multiple mass lesions in the liver; peritonitis carcinomatosa – the appearance of intraperitoneal tumours with malignant ascites (cytological examinations were done if necessary); and lymph node recurrence – the appearance of swelling lymph nodes along the abdominal aorta, superior mesenteric, coeliac or common hepatic artery. Survival was calculated from the time of surgical resection to death or the most recent contact.

Statistical analysis was carried out with the χ^2 test. Actuarial survival curves were constructed using the Kaplan–Meier method[14], and differences between them were assessed with the log rank test. Logistic regression analysis was used to evaluate risk factors for liver metastasis[15], and Cox proportional hazards analysis was performed to evaluate survival[16]. $P < 0{\cdot}05$ was considered statistically significant.

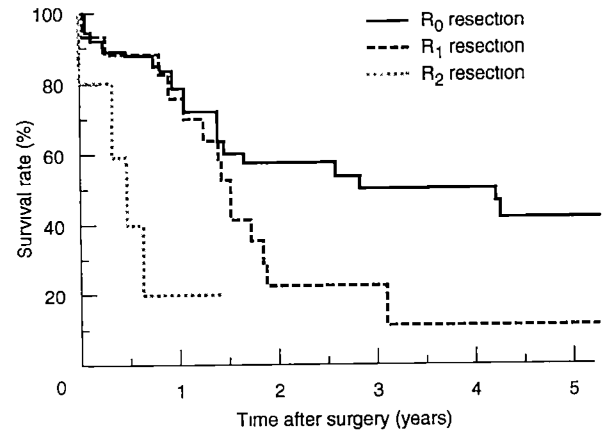
Results

Histologically, differentiated adenocarcinoma (67 per cent) was noted most frequently, followed by poorly differentiated adenocarcinoma (16 per cent). Papillary adenocarcinoma was found in 13 per cent of patients. Adenosquamous cell carcinoma and undifferentiated carcinoma were found in 3 and 1 per cent of patients respectively. Histopathological tumour staging and operative procedures are shown in *Table 1*.

Table 1 Summary of pathological tumour node metastasis staging and operative procedure

		Operative procedure			
pTNM stage	No. of patients	PD	PPPD	REBD	TP
I	4 (6)	2	2	0	0
II	12 (19)	6	3	3	0
III	5 (8)	4	1	0	0
IVa	40 (62)	19	19	1	1
IVb	3 (5)	2	0	1	0
Total	64 (100)	33	25	5	1

Values in parentheses are percentages. pTNM, pathological tumour node metastasis, PD, standard pancreaticoduodenectomy, PPPD, pylorus-preserving pancreaticoduodenectomy; REBD, resection of extrahepatic bile duct, TP, total pancreatectomy



No at risk	0	1	2	3	4	5
R_0	42	33	19	15	13	10
R_1	17	13	4	2	1	1
R_2	5	1	0	0	0	0

Fig. 1 Actuarial 5-year survival curves for patients with distal bile duct cancer according to the residual cancer (R) classification. $P = 0{\cdot}02$ (R_0 *versus* R_1 resection, log rank test)

The overall actuarial 5-year survival rate was 32 per cent. Of four patients with stage I disease, all were alive at 5 years; three of 12 patients with stage II were alive at 5 years; one of five with stage III; three of 40 with stage IVa; and none of three patients with stage IVb. There were no differences in 5-year survival between the PPPD and the standard pancreaticopancreatectomy groups. Actuarial 5-year survival rates of R_0, R_1 and R_2 groups were 43 per cent of 42 patients, 12 per cent of 17, and none of five respectively (*Fig. 1*).

Various modes of tumour recurrence were identified. Liver metastases were observed in 21 patients (33 per cent), lymph node metastases in six (9 per cent), peritoneal metastases in six (9 per cent) and local recurrence in two (3 per cent). The liver recurrence rate was significantly higher than recurrence at other sites ($P < 0{\cdot}05$). On the other hand, liver metastasis was revealed to be as frequent in the R_0 group (14 of 42) as in the R_1 group (six of 17) (*Table 2*). However, lymph node and peritoneal recurrences in the R_0 group were significantly lower than those in the R_1 group (*Table 2*).

To determine the influence of postoperative adjuvant chemotherapy on liver recurrence, liver recurrence rates were compared in patients who received chemotherapy (30 patients) and those who did not (12) following R_0 resection. There was no significant difference between the two groups.

By univariate analysis, the predictive factors of long-term outcome were microscopic lymphatic involvement, microscopic vascular involvement, microscopic perineural

Table 2 Mode of recurrence related to the residual tumour classification after resection

	R_0 (n = 42)	R_1 (n = 17)	R_2 (n = 5)	Total (n = 64)
Liver recurrence				
Absent	28	11	4	43 (67)
Present	14	6	1	21 (33)
Lymph node recurrence				
Absent	41	14	3	58 (91)
Present	1*	3	2	6 (9)
Peritoneal recurrence				
Absent	40	13	4	57 (89)
Present	2†	4	1	7 (11)

Values in parentheses are percentages. $^*P < 0{\cdot}05$ *versus* presence of lymph node metastasis in R_1 resection group, $^\dagger P < 0{\cdot}05$ *versus* presence of peritoneal metastasis in R_1 resection group (χ^2 test)

Table 3 Clinicopathological findings related to the presence of liver metastasis

	Liver metastasis Absent (n = 43)	Liver metastasis Present (n = 21)	P‡
Tumour location			
Lower third	21	10	0·316
Lower and middle third	18	11	
Middle third	4	0	
Histology (G grading*)			
Papillary adenocarcinoma	7	1	0·056
Well differentiated (G_1)	21	4	
Moderately differentiated (G_2)	9	9	
Poorly differentiated (G_3)	5	5	
Other†	1	2	
Lymph node metastasis			
Absent	27	12	0·663
Present	16	9	
Pancreatic invasion			
Absent	25	11	0·662
Present	18	10	
Duodenal invasion			
Absent	36	12	0·021
Present	7	9	
Microscopic perineural invasion			
Absent	15	1	0·009
Present	28	20	
Microscopic lymphatic involvement			
Absent	16	3	0·059
Present	27	18	
Microscopic vascular involvement			
Absent	26	3	< 0·001
Present	17	18	

*Histopathological grading based on tumour node metastasis classification[12]. †Includes two adenosquamous cell carcinomas and one undifferentiated carcinoma. ‡χ^2 test

Table 4 Factors influencing survival in distal bile duct cancer

Prognostic variable	Hazard ratio	P^*
Overall ($n = 59$)		
Age > 65 years	2·57 (1·21–5·46)	0·014
Lymph node metastasis	2·73 (1·35–5·52)	0·005
Microscopic vascular involvement	2·82 (1·34–5·90)	0·006
R_0 resection group ($n = 39$)		
Microscopic vascular involvement	4·42 (1·52–12·8)	0·006

Values in parentheses are 95 per cent confidence intervals. In-hospital deaths were excluded from this analysis ($n = 5$) *Cox proportional hazards analysis

invasion, lymph node metastasis, pancreatic invasion, duodenal invasion and age greater than 65 years.

In patients with liver recurrence, the incidence of duodenal invasion, microscopic perineural invasion, microscopic lymphatic involvement and microscopic vascular involvement was higher than in those without these findings, but there was no significant difference in the incidence of liver metastases in patients with lymph node metastasis (*Table 3*).

Logistic regression analysis showed that the only independent risk factor for liver metastasis was microscopic vascular involvement (odds ratio 2·71, $P = 0·007$).

Independent prognostic factors relative to patient survival were microscopic vascular involvement, age greater than 65 years and lymph node metastasis after exclusion of in-hospital deaths ($n = 5$) in a Cox regression model (*Table 4*). In addition, microscopic vascular involvement was the only independent factor affecting survival after R_0 resection (*Table 4*).

Discussion

Surgical resection is the only treatment modality that can provide a potential cure for periampullary carcinoma, including distal bile duct cancer. Resectability and survival rates are high compared with those in patients with cancer of the proximal bile duct and pancreatic head, and pancreaticoduodenectomy has been recommended as a safe and curative procedure[17,18].

In this study a retrospective analysis was made of results in 64 patients with distal bile duct cancer to examine the relationship between modes of recurrence and survival following curative resection. Resectability and overall 5-year survival rates were 91 and 32 per cent respectively, being similar to values obtained (91 and 28 per cent) in a recent large series from Johns Hopkins[13]. In a collection of several recent series[8], the mean 5-year survival rate was 24 (range 0–52) per cent for patients with distal bile duct cancer. Survival in patients with distal bile duct cancer is not as high as in those with pancreatic cancer, even though the chance of curative resection is higher for distal bile duct cancer than for pancreatic cancer[1,11,19].

According to the TNM classification of malignant tumours[12], the grade of surgical treatment for malignant tumours is strictly defined in the R classification. This definition in the surgical procedure is dependent on the degree of nodal dissection and the status of duodenal, hepatic and resection margins. In the present study, R_0 resection resulted in a higher survival rate in patients with distal bile duct cancer than in those having R_1 and R_2 resections, indicating the surgical significance of the R classification.

The liver recurrence rate after R_0 resection was as high as that after R_1 resection, although the lymph node and peritoneal recurrence rates were much lower than those following R_1 or R_2 resection. This suggests that, even when R_0 resection with extensive lymph node dissection was performed, liver recurrence could not be prevented. Lymph node metastasis, microscopic perineural invasion, pancreatic invasion and duodenal invasion were significant negative factors for survival after resection, both in this study and in several recent reports[1,11,17,20]. In the present study, however, the independent negative prognostic factors by multivariate analysis were older age, lymph node metastasis and microscopic vascular involvement. Only microscopic vascular involvement was a prognostic factor after R_0 resection. These results suggest that the high rate of liver recurrence after R_0 resection may be related to microscopic vascular involvement.

Several studies have shown a correlation between microvessel count and liver metastasis in patients with gastric[21], colorectal[22] or oesophageal[23] cancer. In recent years, vascular endothelial growth factor[21,24] and thymidine phosphorylase[25] as angiogenesis factors have been shown to be linked to angiogenesis and haematogenous metastatic propensity. A previous report[26] demonstrated that the expression of thymidine phosphorylase in tumours correlated significantly with the presence of postoperative liver metastases and a poorer prognosis in patients with invasive ductal carcinoma of the pancreas. These reports raise the possibility that these angiogeneses are necessary for bile duct cancer to produce liver metastasis.

In conclusion, the optimal therapy for a patient with distal bile duct cancer is R_0 resection of the lesion. However, R_0 resection does not necessarily signify better survival, because of liver metastasis. Microscopic vascular involvement is not only associated with liver metastasis, but is also an independent prognostic factor after R_0

resection for distal bile duct cancer. Postoperative adjuvant therapy with new agents such as angiogenesis inhibitors, or strategies to prevent liver metastasis, should be considered to improve survival rates.

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Factors influencing survival of patients undergoing hepatectomy for colorectal metastases

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Background: The extent of surgical margin is still a matter of controversy with regard to outcome after liver resection for metastatic disease. The aim of this study was to clarify the significant prognostic factors after hepatectomy for colorectal metastases, with special reference to the surgical margin.
Methods: Ninety-six patients who underwent initial hepatic resection for liver metastases from colorectal cancer between 1992 and 1994 were studied.
Results: Overall 1-, 3- and 5-year survival rates were 94, 61 and 51 per cent respectively. All of the independent factors associated with poor prognosis after hepatic resection were tumour-related factors, such as the number of tumours (four or more), presence of portal vein invasion, hepatic vein invasion and absence of a fibrous pseudocapsule. A positive resection margin was not an independent prognostic factor, because of its strong relationship with the number of tumours resected.
Conclusion: A generous surgical margin is not essential for curative hepatic resection, although positive surgical margins should be avoided. New potential risk factors which affect survival, such as the presence of portal vein or hepatic vein invasion and the absence of a pseudocapsule, may be helpful for defining the indications for postoperative adjuvant treatment.

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Introduction

Many studies have attempted to define prognostic factors after hepatic resection in patients with colorectal liver metastases[1–13]. The extent of the surgical margin is still a controversial prognostic factor for survival after liver resection for metastatic disease[2–7,10–13]. A previous study of the clinicopathological features of metastatic lesions of colorectal cancers revealed an affinity for the portal pedicle and the rarity of intrahepatic metastasis of these metastatic tumours[14]. From these pathological characteristics of metastatic lesions, it did not seem necessary to secure a surgical margin of 1 cm because there were no microscopic deposits in the parenchyma, even within 10 mm of the metastatic tumours. In the present report, the clinicopathological factors were reviewed in a larger series of patients, and the relationship between these factors and their contribution to the prognosis after liver resection was analysed.

Patients and methods

Between 1992 and 1994, 122 patients underwent hepatic resection for treatment of colorectal liver metastases and were followed for at least 2 years. Twenty-six patients (21·3 per cent) underwent repeat resection of recurrent liver tumours, of whom 20 underwent a second liver resection, four a third resection and two a fourth resection. For this report 96 patients who underwent initial hepatectomy in this unit were selected (38 patients received primary colorectal surgery in other hospitals). During the same period, 111 patients who underwent surgery for primary colorectal disease in this hospital were diagnosed with colorectal liver metastases (66 patients with synchronous lesions and 45 with metachronous lesions), and 58 underwent liver resection. The overall rate of resectability was thus 52·3 per cent (58 of 111); 28 (42 per cent) of 66 synchronous metastases and 30 of 45 metachronous lesions.

No patient died either within 1 month after surgery or during the initial hospital stay. Two patients underwent concomitant resection of other malignancies at the time of hepatectomy: one was for local recurrence of the primary rectal cancer and one for synchronous primary lung cancer. After surgery, follow-up data were obtained by visits or from patient's physician records. Follow-up ranged from 5·7 to 65·3 (median 37·6) months.

Factors analysed

The variables were selected by consideration of their potential relationship to survival after hepatectomy as indicated by previous studies[1–13]. The pathological factors of intrahepatic extension of the metastatic nodules were added. The following preoperative demographic and clinical information was obtained from the patient records: age, sex, temporal relationship of metastases with primary disease (synchronous or metachronous) and operative procedure. The operative procedure was classified as follows: major hepatectomy, bisegmentectomy and more extended hepatectomy; and minor hepatectomy, all resections less extensive than bisegmentectomy. All metastatic nodules were evaluated for the purpose of collecting pathological data. Macroscopic findings of surgical specimens included the number, size (maximum tumour diameter), location, gross extension pattern of the tumours and the width of the surgical margins. Microscopic features evaluated were histological differentiation; the presence of invasion of the portal vein, intrahepatic bile duct, nerve, hepatic vein, fibrous pseudocapsule between tumours and the liver parenchyma; and cancer cells at the surgical margin. The histological type of the tumours was determined according to the classification of the World Health Organization[15]. The margin of resection was classified as: (1) histologically negative and 1 cm or more in width; (2) histologically negative and less than 1 cm in width; and (3) histologically positive. In patients with multiple metastases, the pathological findings of the largest tumour represented those of the other tumours. However, margins of all metastatic nodules were studied and the shortest distance was selected as the surgical margin for each patient. When one lesion among multiple tumours was exposed, the patient was defined as having a positive surgical margin.

Statistical analysis

The trends and differences in proportions were tested by the Mantel–Haenszel χ^2 test[16]. Survival estimates were calculated by the Kaplan–Meier method[17], and were compared using the log rank test. The Cox proportional hazards model was used to adjust co-variates[18]. All variables were dichotomized for analysis. Significance was defined as $P < 0{\cdot}05$.

Results

Clinicopathological data

The patient characteristics are shown in *Table 1*. The primary tumour site was the rectum in 34 patients, the sigmoid colon in 35, the descending colon in seven, the transverse colon in five, the ascending colon in seven and the caecum in five. Three patients had double primary tumours of the transverse and sigmoid colon, the descending and sigmoid colon, and the sigmoid colon and rectum, respectively. Thirty-nine patients (41 per cent) had a solitary tumour, 19 (20 per cent) had multiple unilobar tumours and 38 (40 per cent) had multiple bilobar tumours. Satellite metastases were seen in four patients (4 per cent). The mean maximum diameter of the tumours was 4·3 (range 0·9–12·5) cm.

Survival analysis

Overall 1-, 3- and 5-year survival rates were 94, 61 and 51 per cent respectively (*Table 1*). When the cumulative survival rate was compared among the various subgroups identified by each predictive factor, number of metastases (four or more), bilobar tumour distribution, presence of portal venous invasion, neural/perineural invasion and hepatic vein invasion, absence of a fibrous pseudocapsule and a positive resection margin were found to be significantly related to a poor outcome after surgery (*Table 1*). Patients with four or more nodules showed significantly worse survival than those with fewer tumours (*Fig. 1*).

With regard to the width of surgical margin, a narrower resection margin had an adverse effect on patient survival (*Fig. 2*). Patients with a margin wider than 1 cm tended to have a better survival rate than those with a margin of 1 cm or less.

When the significant prognostic factors in univariate analysis were assessed by multivariate analysis, the following factors were found to be independently associated with poor survival: four or more tumours, presence of portal vein invasion, hepatic vein invasion and absence of pseudocapsule with hazard ratios (95 per cent confidence interval) of 2·62 (1·08–6·35), 2·27 (1·16–4·46), 2·90 (1·26–6·66) and 1·79 (0·90–3·55) respectively. Bilobar tumour, neural/perineural invasion and involved surgical margin were not significant in a multivariate context.

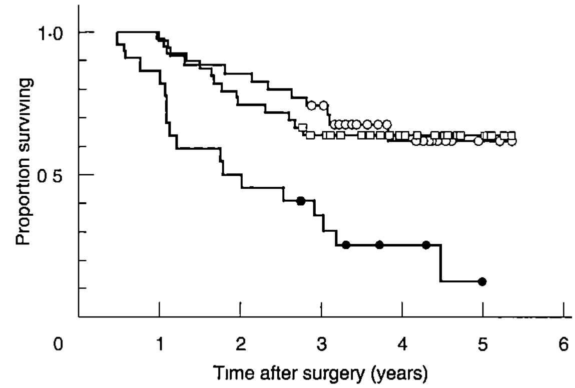
Table 1 Clinical, pathological and treatment-related factors for survival after hepatectomy

	No. of patients	Proportion surviving (%) 1 year	3 years	5 years	*P*
Overall	96 (100)	94	61	51	
Age (years)					
< 60	45 (47)	91	58	55	n.s.
≥ 60	51 (53)	96	64	47	
Sex					
M	64 (67)	92	65	55	n.s.
F	32 (33)	97	53	42	
Temporal relationship					
Synchronous	28 (29)	96	45	36	n.s.
Metachronous	68 (71)	93	68	57	
No. of metastases					
1	39 (41)	97	74	64	n.s.†
2–3	35 (36)	97	64	64	0·0009‡
4 or more	22 (23)	82	36	13	0·0003§
Tumour distribution in the liver					
Unilateral	56 (58)	96	68	62	0·03
Bilateral	40 (42)	90	52	35	
Tumour size (cm)					
< 5	63 (66)	95	65	54	n.s.
≥ 5	33 (34)	91	53	46	
Histological differentiation					
Well	48 (50)	96	60	48	n.s.
Moderate*	48 (50)	92	62	56	
Portal vein invasion					
Absent	71 (74)	97	67	60	0·004
Present	25 (26)	84	44	29	
Intrahepatic bile duct invasion					
Absent	56 (58)	93	59	50	n.s.
Present	40 (42)	95	65	55	
Neural or perineural invasion					
Absent	80 (83)	96	66	57	0·004
Present	16 (17)	81	38	23	
Hepatic vein invasion					
Absent	87 (91)	95	64	57	0·001
Present	9 (9)	78	33	0	
Fibrous pseudocapsule					
Absent	37 (39)	92	43	19	0·03¶
Thin	31 (32)	90	64	61	n.s.**
Thick	28 (29)	95	73	71	0·0001††
Surgical procedure					
Minor resection	73 (76)	93	64	58	n.s.
Major resection	23 (24)	96	52	32	
Resection margin					
> 1 cm	19 (20)	100	78	73	n.s.‡‡
≤ 1 cm	60 (62)	95	58	56	0·02§§
Involved	17 (18)	82	47	18	0·003¶¶

Values in parentheses are percentages. *Includes two patients with poorly differentiated adenocarcinoma. n.s., Not significant. †Solitary *versus* 2–3 metastases, ‡2–3 *versus* 4 or more metastases, §solitary *versus* 4 or more metastases, ¶absent *versus* thin, **thin *versus* thick, ††absent *versus* thick, ‡‡resection margin >1 *versus* ≤1 cm; §§involved *versus* ≤1 cm; ¶¶involved *versus* >1 cm (log rank test)

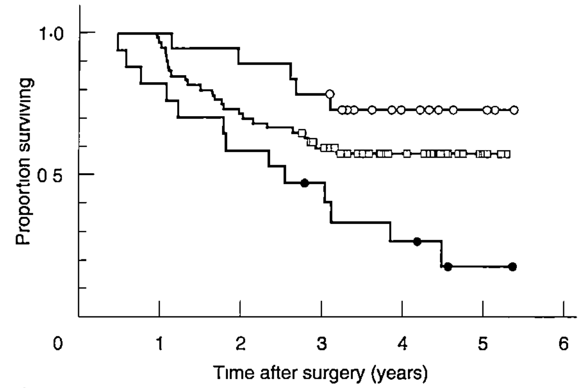
Relationship between resection margin and other factors

By Mantel–Haenszel χ^2 analysis, the width of resection margin was strongly associated with the number of tumours and the tumour distribution in the liver. The histological differentiation and the state of the fibrous pseudocapsule showed a marginally significant association (*Table 2*).



No. at risk						
1	39	38	29	22	14	6
2–3	35	34	30	24	11	2
≥ 4	22	18	11	7	3	1

Fig. 1 Survival after initial hepatic resection in patients with one ($n = 39$; ○), two to three ($n = 35$; □) or more than three ($n = 22$; ●) metastases. The difference in survival was not significant between the patients with a solitary lesion and those with two or three lesions ($P = 0·77$) The patients with four or more metastases showed a significantly poorer survival than those with a solitary lesion ($P = 0·0009$) or with two or three metastases ($P = 0·0003$) (log rank test)



No. at risk						
> 1 cm	19	19	17	15	7	3
≤ 1 cm	60	57	43	24	17	5
Involved	17	14	10	7	4	1

Fig. 2 Survival after initial hepatic resection in patients with a resection margin of more than 1 cm ($n = 19$; ○), 1 cm or less ($n = 60$; □) or an involved margin ($n = 17$; ●). Patients with a surgical margin of more than 1 cm tended to show better survival than those with a histologically negative margin of less than 1 cm ($P = 0·18$). Patients with a positive surgical margin had significantly worse survival than those with a margin of more than 1 cm ($P = 0·003$) or less than 1 cm ($P = 0·02$) (log rank test)

Discussion

In this study, a cancer-involved surgical margin was not an independent prognostic factor owing to its strong association with the number of tumours. A narrow surgical margin reportedly has an adverse effect on patient outcome after surgery[2,3,5,6,12,13], especially when it is involved by the tumour[4,10,11], and many surgeons have advocated that hepatectomy with a sufficient margin of more than 1 cm is necessary for the surgical therapy of colorectal liver metastases[1,5,7,9,12,13]. However, a policy of a margin of 1 cm or more for curative resection might limit the application of surgical therapy for liver metastases. The resection rate of metastatic colorectal carcinoma reportedly varies from 22 to 31 per cent[5,19,20], which was lower than that in the present series (52·3 per cent). Multiple resections of bilateral tumours are required to preserve non-cancerous liver tissue by securing the portal tracts and thus provide liver transection planes close to the tumour margin. In the present series, of 17 patients with a positive margin, nine had four or more metastases and 14 had multiple bilobar metastases. Overall survival for the patients with three or fewer tumours ($n = 74$) was similar between 66 patients with a clear margin and eight with a positive margin. In addition, microscopic satellite deposits were not found in the parenchyma within 1 cm from gross metastatic tumours either in the present series or in a previous study[14]. Thus, securing a margin of more than 1 cm for metastatic colorectal cancer cannot be justified on an oncological basis.

In the present study, all of the independent prognosticators were tumour-related factors. The presence of four or more metastases is a potential adverse prognostic factor[1–3,8,11]. The presence of portal vein invasion was another potential prognostic factor for poor survival. In the case of hepatocellular carcinoma (HCC), portal venous invasion indicates that the tumour has an invasive propensity, and shows a very strong association with the presence of intrahepatic metastases, which supports the notion of intrahepatic spread of HCC via the portal venous system[21–23]. However, in this series of colorectal liver metastases, the distribution of gross tumours in the liver did not appear to be on a segmental basis, as observed in the case of HCC[23]. Multiple tumours were more frequently distributed in both lobes (40 per cent) than in a single lobe (20 per cent). Positive portal vein invasion was not associated with multiple tumours. A satellite configuration of the lesions, which indicates step-by-step intrahepatic dissemination of the tumours, has been reported to be present in about 15 per cent of resected cases[2,5], but occurred in only 4 per cent in this study. Multiple colo-

Table 2 Relationship between resection margin and other clinicopathological factors

Factor	Width of resection margin			P^*
	>1 cm	≤ 1 cm	Involved	
Age (years)				
<60 ($n = 45$)	11 (24)	25 (56)	9 (20)	n.s.
≥ 60 ($n = 51$)	8 (16)	35 (69)	8 (16)	
Sex				
M ($n = 64$)	12 (19)	40 (62)	12 (19)	n.s.
F ($n = 32$)	7 (22)	20 (62)	5 (16)	
Temporal relationship				
Synchronous ($n = 28$)	5 (18)	16 (57)	7 (25)	n.s
Metachronous ($n = 68$)	14 (21)	44 (65)	10 (15)	
No of metastases				
1–3 ($n = 74$)	18 (24)	48 (65)	8 (11)	0·0008
4 or more ($n = 22$)	1 (5)	12 (55)	9 (41)	
Tumour distribution in the liver				
Unilateral ($n = 56$)	15 (27)	36 (64)	5 (9)	0·003
Bilateral ($n = 40$)	4 (10)	24 (60)	12 (30)	
Tumour size*				
< 5 cm ($n = 63$)	12 (19)	40 (63)	11 (17)	n.s
≥ 5 cm ($n = 33$)	7 (21)	20 (61)	6 (18)	
Histological differentiation				
Well ($n = 48$)	7 (15)	29 (60)	12 (25)	0·047
Moderate or poor ($n = 48$)	12 (25)	31 (65)	5 (10)	
Portal vein invasion				
Absent ($n = 71$)	14 (20)	45 (63)	12 (17)	n.s
Present ($n = 25$)	5 (20)	15 (60)	5 (20)	
Intrahepatic bile duct invasion				
Absent ($n = 56$)	11 (20)	37 (66)	8 (14)	n.s
Present ($n = 40$)	8 (20)	23 (58)	9 (22)	
Neural or perineural invasion				
Absent ($n = 80$)	19 (24)	48 (60)	13 (16)	0·054
Present ($n = 16$)	0 (0)	12 (75)	4 (25)	
Hepatic vein invasion				
Absent ($n = 87$)	18 (21)	55 (63)	14 (16)	n.s.
Present ($n = 9$)	1 (11)	5 (56)	3 (33)	
Fibrous pseudocapsule				
Absent ($n = 37$)	3 (8)	26 (70)	8 (22)	0·049
Present ($n = 59$)	16 (27)	34 (58)	9 (15)	
Extent of resection				
Minor resection ($n = 73$)	13 (18)	47 (64)	13 (18)	n.s.
Major resection ($n = 23$)	6 (26)	13 (57)	4 (17)	

Values in parentheses are percentages n.s., Not significant. *Mantel–Haenszel χ^2 test

rectal liver metastases are more probably derived from multiple metastatic foci from the primary disease than from intrahepatic remetastasis of the liver lesion. Hepatic vein invasion, which was seen less frequently than that of the portal vein, was another potential prognosticator.

The presence of a pseudocapsule was associated with better survival after liver resection. A fibrous capsule is the most frequent gross characteristic of HCC, and indicates an expanding growth pattern and better prognosis compared with that of an infiltrating tumour without capsule formation[24,25]. These peritumoral desmoplastic reactions require consideration in postoperative follow-up planning and treatment. Tumour size, which was reported to be a potential prognostic factor and to have a relationship with invasion to the portal vein and bile duct[13], was not a significant prognosticator and had no association with other factors of invasion in this series.

Hepatectomy can be applied to a larger proportion of patients with colorectal liver metastases without jeopardizing the outcome after resection by a combination of minor resections. Clearly a positive surgical margin implies the presence of microscopic residual cancer cells and thus should be avoided. However, a generous surgical margin is not a necessary condition for curative hepatic resection. This analysis of the pathological features of metastatic deposits may be useful for determining postoperative adjuvant treatment and follow-up.

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Effect of exercise on calf muscle pump function in patients with chronic venous disease

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Background: Musculoskeletal dysfunction may be associated with poor calf muscle pump function in patients with chronic venous ulceration. The aim of this study was to evaluate the effects of physical exercise on calf muscle pump function.
Methods: Twenty patients were recruited into a 6-week intensive exercise programme. Calf muscle function and calf muscle pump function were assessed using an isokinetic device and air plethysmography respectively, before and after the exercise programme.
Results: There was significant improvement in calf muscle pump function, measured as increased ejection fraction and decreased residual fraction ($P < 0{\cdot}05$); however, venous reflux was not altered ($P > 0{\cdot}05$). Calf muscle strength and endurance parameters all increased, but not significantly ($P > 0{\cdot}05$).
Conclusion: Poor calf muscle pump function in patients with chronic venous ulceration can be improved by physical exercise.

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Introduction

Calf muscle pump failure is considered to be the main aetiological factor in patients with chronic venous ulceration[1]. Previous studies have shown that patients with venous ulceration have histopathological changes of degeneration in the calf muscle[2]. Arthropathy with a limited range of motion at the ankle is a significant factor[3]. Previous studies in this department have shown that patients with venous ulcers have impaired calf muscle function[4]. These studies suggest collectively that musculoskeletal dysfunction of the leg is associated with poor function of the calf muscle pump. There are few data showing the influence of physical exercise on calf muscle pump function in patients with chronic venous insufficiency[5]. The purpose of this pilot study was to evaluate the effects of physical exercise on calf muscle pump function in patients with chronic venous insufficiency.

Patients and methods

Patients

Twenty patients with recently healed venous ulceration (20 legs) were recruited into the study from the Leg Ulcer Clinic at Fremantle Hospital. There were seven women and 13 men, of median age 68 (range 34–88) years. All patients were mobile without evidence of arterial insufficiency on Doppler pressure measurement and with no limitation of ankle motion. All patients had both deep and superficial veins assessed by duplex imaging. The presence of reflux was defined as a reflux duration of more than 0·5 s. The presence or absence of venous obstruction was determined by duplex imaging. Failure of the duplex signal to augment with distal compression of the veins was taken as evidence of venous obstruction. Results of duplex imaging and the 'CEAP' (clinical manifestations, aetiological factors, anatomic involvement, pathophysiological features) classification[6] of the venous disease are listed in *Fig. 1*. Patients did not wear compression bandages or stockings during the exercise programme.

This study was approved by the Human Rights Committee of the University of Western Australia, and informed consent was obtained from each patient.

Exercise programme

An intensive exercise programme specifically tailored for each patient was used. The exercise comprised heel rises (tip-toe exercise). The programme was carried out in the home, and the training was monitored by medical research staff. The exercise routine was as follows: the patient

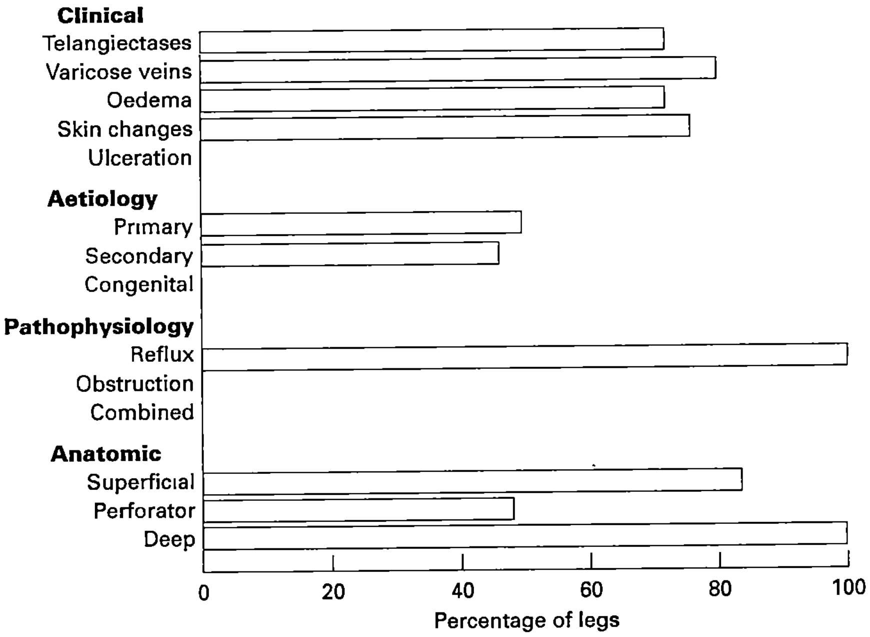

Fig. 1 CEAP classification of the 20 legs of patients with venous disease

started by standing in an upright position with the balls of the feet on the edge of a step 5 cm high. The patient slowly lowered the heels to the floor, and then raised them as far as possible. During the exercise, it was recommended that the patient held a rail or the back of a chair to help balance.

Before commencing the exercise programme, patients were assessed individually to determine the maximum number of tip-toe exercises that they could perform. Patients exercised on alternate days for 6 weeks. At each exercise session during the first 3 weeks, patients were asked to perform three repetitions of half of their maximum number of tip-toe exercises. During the second 3 weeks, the patients were programmed to increase the number of tip-toe exercises, to the maximum number that they could perform at the initial testing, and again to perform three repetitions of these exercises. Patients were instructed to rest for 3–5 min between repetitions. Before starting and after each exercise session, patients were recommended to perform warming up and cool down activities, which included 5–8 min of walking combined with calf stretch exercises.

Calf muscle function

A Biodex System 2 Multi-Joint Testing and Rehabilitation System (Biodex Medical System, Shirley, New York, USA) with Biodex Advantage Software 3.0 (Biodex Advance Software; Biodex, NewYork, USA) was used for assessing calf muscle function. The testing procedures have been reported in detail previously[4].

To test calf muscle strength, all patients were asked to complete five maximal ankle dorsiflexion and plantar flexion movements at the angle velocity of 60° per s; the tests were performed in triplicate. Peak torque (PT), the ratio of PT to body-weight (BW) and average power (AP1) were measured. The results were calculated based on the mean of three repeated measurements of ankle plantar flexion. To test muscle endurance, the same test setting was used for 25 repetitions of ankle dorsiflexion and plantar flexion at an angle velocity of 120° per s. Total work (TW) and average power (AP2) of ankle plantar flexion were obtained to measure the absolute endurance of calf muscles. The assessments were performed before and after the 6-week exercise programme.

The variability of these measurements in repeated testing and their reproducibility in test–retest situations has been assessed previously. The coefficients of variation (CV) for repeated measurements of PT and PT/BW ranged from 2·5 to 22·1 per cent, and that for the measurement of average power (AP1) was 14·6 per cent. The CV of method error (CV_{ME}) for test–retest reproducibility of performing measurements on different days were approximately 16 per cent for PT, PT/BW and AP1. However, the CV_{ME} for muscle endurance-measuring parameters of TW and AP2 were 22 5 and 27·9 per cent respectively[4].

Table 1 Comparison of calf muscle function in patients before and after 6 weeks of exercise

	Before exercise	After exercise	*P**
Muscle strength (60° per s)			
Peak torque (Nm)	15·0 (11·8–23·2)	21·0 (14·5–29·6)	0·251
Peak torque/body-weight (%)	21·5 (12·1–29·9)	25·1 (17·9–35·8)	0·184
Average power 1 (W)	8·6 (3·7–11·7)	9·5 (6·7–14·0)	0·546
Muscle endurance (120° per s)			
Total work (Nm)	155·1 (76·8–173·4)	157·0 (108·3–239·0)	0·629
Average power 2 (W)	12·0 (5·5–15·5)	12·3 (8·6–15·6)	0·936

Values are median(interquartile range) *Wilcoxon matched-pairs signed ranks test

Table 2 Comparison of calf muscle pump function before and after 6 weeks of exercise

	Before exercise	After exercise	*P**
Venous volume (ml)	128·8 (87·7–158·9)	123·2 (78·5–150·6)	0·279
Ejection fraction (%)	57·8 (39·5–64·8)	69·5 (59·2–99·6)	0·001
Venous filling index (ml/s)	5·9 (5·1–11·2)	6·3 (4·6–9·2)	0·351
Residual fraction (%)	57·7 (43·5–75·3)	34·1 (21·5–52·1)	0·001

Values are median(interquartile range). *Wilcoxon matched-pairs signed ranks test

Calf muscle pump function

Calf muscle pump function was assessed by air plethysmography (APG). The APG machine consisted of a tubular, polyurethane air cuff (capacity 5 litres) (ACI Medical, Sun Valley, California, USA) that enclosed the whole leg from knee to ankle, a pressure transducer, a cuff inflator air pump, an amplifier and a recorder (LR8100, model 3701; Yokogawa, Tokyo, Japan). The detailed testing procedure and reproducibility of measurement have been reported previously[7,8]. In this study, 90 per cent venous filling time (VFT), venous filling index (VFI), venous volume (VV), venous ejection volume, venous ejection fraction (EF), residual volume and residual fraction (RF) were measured. As with calf muscle function assessment, the tests were performed in triplicate before and after the exercise programme. The results were based on the mean of three repeated measurements.

Statistical analysis

The Wilcoxon matched-pairs signed rank test was used to compare calf muscle function and calf muscle pump function before and after the exercise programme.

Results

All patients completed the 6-week exercise programme without any adverse effects.

Calf muscle function

After the 6-week exercise programme, there was no significant change in any of the muscle strength or endurance parameters, although for all parameters the mean value after 6 weeks of exercise was greater than the starting value (*Table 1*). The mean calf muscle strength, measured as PT, PT/BW and AP1, had increased by approximately 20 per cent; endurance, measured as TW and AP2 of 25 repetitions of ankle plantar flexion, appeared to have increased by about 10 per cent. The increase in strength parameters was slightly larger than the test–retest variation, whereas the increase in endurance parameters was only approximately half of the test–retest variation.

Calf muscle pump function

After 6 weeks of exercise, calf muscle pump function had significantly improved, with increased EF and decreased RF ($P = 0{\cdot}001$) (*Table 2*). However, there was no significant difference in venous refilling (VFI) or VV.

Discussion

Physical exercise is valuable in patients with peripheral arterial disease[9–11]. The haemodynamic effects of physical exercise on the arterial circulation are well documented[12,13]. In contrast, the influence of physical exercise on the venous circulation has been largely ignored. This study indicated that calf muscle pump function in patients with chronic venous insufficiency is improved by physical exercise. The EF, which measures the capacity of the outflow of the calf muscle pump, was significantly increased at the end of 6 weeks of exercise. The lack of change in venous refilling (VFT and VFI) and VV suggests that the improvement in EF is likely to be associated with strengthening of the calf muscles rather than improvement in venous function.

The function of calf muscles increased by 10–20 per cent after the exercise programme in this study; however, these changes were not statistically significant. This is consistent with previous studies[14], which reported that leg muscle strength can be increased and that improvement ranges from less than 10 per cent to 72 per cent. The subjects in previous studies were all in reasonably good health, in contrast to those in this study who had chronic venous disease. The present data suggest that leg muscle strength and endurance could be improved by physical exercise regardless of the presence of chronic venous disease. The failure to show a significant change in muscle function could result from a number of factors, including the small sample size, the large variability in muscle function parameters and the short duration of the exercise programme. A larger sample size might help to avoid a type II error in asssessing muscle strength. A longer exercise programme could also help determine whether improvements in muscle strength that are implied by the improvement in EF and RF have actually occurred.

A well designed exercise programme is thought to be the most important factor effecting exercise outcome[15]. The tip-toe exercise was chosen because it directly strengthens the calf muscles which are the target muscle group involved in the calf muscle pump. This particular exercise is also part of the APG test and if the exercise programme itself did improve muscle pump function, it should therefore be possible to measure it. Consideration was also given to avoiding sustained intense or prolonged effort, because other medical problems could arise under these conditions[15]. In the present study, these two issues were considered together, and an individualized exercise programme was developed which could be easily carried out at home, and was acceptable to all participants. There were no exercise-related incidents recorded in this study and all participants completed the 6-week exercise programme as scheduled.

This study was a single-arm pilot study and the exercise programme was performed soon after the patients' leg ulcers had healed. The improvement in calf muscle pump function could possibly have been related to healing of the ulcer and not directly to the exercise programme. It will be necessary to carry out further randomized controlled trials to evaluate fully the therapeutic benefit of an exercise programme on muscle strength and calf muscle pump function, and to determine the possible clinical benefits on ulcer healing and the prevention of recurrent venous ulceration.

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Original article

Quantitative study of capillary density in the skin of the foot in peripheral vascular disease

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Background: The aim of this study was to investigate possible differences in capillary density of the skin of the foot between normal subjects and patients with peripheral vascular disease.
Methods: Using *in vivo* video microscopy, a method was developed to measure the average capillary density (ACD) of the skin of the foot and toes. In a cross-sectional observational study, 21 patients with intermittent claudication and 23 patients with rest pain or ischaemic ulceration were compared with 19 age- and sex-matched controls.
Results: Mean(s.e.m). values of ACD of the foot were 33·7(1·9) and 34·4(1·7) per mm^2 in the right and left sides respectively for controls, 31·2(1·8) per mm^2 (P not significant) and 31·9(2·6) per mm^2 (P not significant) in the symptomatic and contralateral sides respectively for patients with claudication, and 22·0(1·8) per mm^2 ($P < 0{\cdot}001$) and 24·3(1·7) per mm^2 ($P < 0{\cdot}001$) in the symptomatic and contralateral sides respectively for patients with rest pain or ulceration.
Conclusion: Capillary density of the skin of the foot is significantly reduced in patients with arterial ulceration compared with that in patients with claudication and healthy subjects.

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Introduction

The pathophysiology of skin ulceration in severe peripheral vascular disease (PVD) remains to be established. Undoubtedly, the haemodynamic disturbance that results from atherosclerotic disease of the large arteries is the fundamental process in the pathogenesis of this condition. The cornerstone of the management of ischaemic ulceration remains revascularization. However, it has become accepted that other systems are also disturbed and that the overall pathophysiology of limb ischaemia represents a multifactorial process involving a complex interaction between macrocirculatory, microcirculatory, haemorrheological and biochemical factors[1–3]. The aim of this work was to explore the role of microcirculatory abnormality in ulceration by undertaking a systemic quantitative analysis of capillary geometry in the skin of the foot of patients with ulceration resulting from PVD compared with healthy subjects and patients with claudication.

Patients and methods

Subjects

The subjects taking part in this work were all inpatients at St George's Hospital Medical School. Approval was given by the local ethics committee at St George's Healthcare NHS Trust, and informed consent obtained from every subject.

Three groups of subjects were defined principally according to the presence and severity of peripheral vascular disease. Group 1 consisted of 19 subjects free from PVD (absence of claudication and skin ulceration, and an ankle : brachial pressure index (APBI) greater than 0·85). They were awaiting or recovering from elective surgery (herniorrhaphy, cholecystectomy, appendicectomy or minor urological or gynaecological procedures) and were matched as far as possible for age and sex to patients in groups 2 and 3. Exclusion criteria were current venous disease of the legs, a history of deep venous thrombosis, any skin disease, any skin trophic changes and autoimmune disorders. The mean age for the group was 67 (range 43–93) years; there were 12 men and seven women. There were six smokers and one diabetic. The mean ABPI of the group was 0·90 (mean of right and left sides).

Group 2 included 21 patients with haemodynamic and radiological evidence of PVD, but whose only symptom was claudication. None of these patients had previously had ulceration of the skin of the foot or rest pain. Other exclusion criteria were the same as for group 1. There were five diabetics and five smokers in this group. The mean age was 68 (range 51–84) years; there were 19 men and two women. Mean values of the ABPI in symptomatic and contralateral legs were 0·55 and 0·74 respectively.

Group 3 consisted of 23 patients with haemodynamic and radiological evidence of PVD, who had skin ulceration in the foot or toes of one or both legs and/or rest pain resulting from their arterial disease. Exclusion criteria included other diseases causing skin ulceration (with the exception of diabetes mellitus) in addition to those of group 1. There were six diabetics and five smokers. The mean values of ABPI in the symptomatic and contralateral legs were 0·28 and 0·60 respectively. The mean age in this group was 76 (range 59–89) years. There were 15 men and eight women.

Measurement of capillary density

Microscopy of skin capillaries was performed using a Wild-Leitz epi-illuminated microscope[4], linked to a video camera (Hitachi CCTV KP-161, Tokyo, Japan). Microscopic images were passed on to a screen (Hitachi VM 921 K) for online monitoring and simultaneously stored on video tape. Subsequently, still-frame video prints were produced by playing back the tape in a separate video recorder linked to a video printer (Sony Multiscan UP 930, Tokyo, Japan). All data analysis was made retrospectively offline from the prints. *In vivo* microscopy relies on the presence of haemoglobin in erythrocytes; all capillaries (i.e. those containing static as well as flowing erythrocytes) are seen. This method therefore measures the total number of capillaries (i.e. 'anatomical' capillary density).

Experimental protocol

Microscopy

The light source was allowed to warm up for 10 min to ensure consistency of light intensity, and the focal settings were adjusted before each procedure so as to produce uniform illumination across the field of interest. The subject sat on a dental chair (Universal couch model 8861, Birmingham, UK), in a room kept at constant temperature (22–24°C), with both feet at 45° dependency; the leg under study was immobilized in a vacuum pillow (Orthopaedic Systems, Edinburgh, UK). A thin film of glycerin oil was applied to the skin to increase its transparency and reduce light reflection. Video microscopy was then performed using the 2·5 × objective (giving a final magnification of exactly 40-fold), at near maximal light intensity. The objective was positioned perpendicular to the skin surface, and the picture was focused and finally recorded on video tape.

Data analysis

The criteria for counting capillaries were first defined according to variability in individual capillary morphology and the plane of focus at microscopy: in the skin of the dorsum of the foot, nutritional capillaries run mostly at a right angle to the skin surface, in the form of 'hairpin' capillary loops. The mean(s.d.) diameters of the arterial and venular limbs of capillary loops were 14(2) and 16(3) μm respectively; this was in agreement with findings from other studies[5]. At microscopy, however, a variety of appearances and a range of dimensions are possible, depending on the plane of focus relative to the capillary, the orientation of the capillary and individual capillary morphological variation. The resulting theoretical microscopic appearances were used as guidelines for counting capillaries[6]. The reproducibility of the procedure was further refined by restricting the analysis of each print to an area within which it was in focus, as it is often not possible to get the whole of the print in focus. For each print a transparent acetate sheet containing rectangular 'boxes' of different areas was placed over the photograph and the appropriate box chosen to cover the largest area in focus within the print (to minimize sampling error). Capillary density was then calculated by dividing the number of capillaries within the box by the area (in mm^2) of the box. Prints in which it was not possible to find an area of satisfactory quality were discarded. These were randomly distributed across the foot of all subjects and were related to such factors as dirt or uneven thickness of the epidermis.

Determination of average capillary density

Recent work has shown significant spatial heterogeneity of capillary density across the foot[7]. Measurement of capillary density at a single random spot on the skin of the dorsum of foot would thus convey little information with respect to the rest of the foot. To reduce the magnitude of such sampling error, it was therefore necessary to take the average of as many readings of capillary density as possible in each case. The foot itself was treated separately from the toes. On the foot, microscopy was performed at 25 positions, in columns and rows spaced at approximately 1-cm intervals on the dorsum of foot. On the toes, microscopy was done at one spot on the proximal and distal phalanges in each toe (*Fig. 1*).

For each foot and set of toes, therefore, 25 and ten values of capillary density respectively were theoretically available. As already noted, some prints had to be discarded because of poor photographic quality and so, in practice, between ten and 25 capillary density values in the

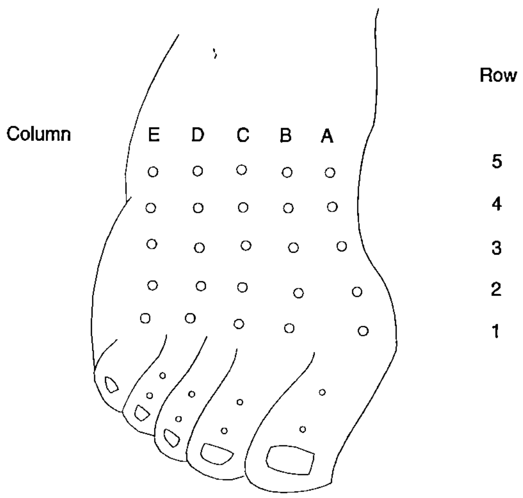

Fig. 1 Positions on the dorsum of the foot and toes at which video microscopy was performed in each subject

foot and five to ten values in the toes were available for analysis. In each case, an average value of capillary density was determined for the foot and toes, representing the average capillary density (ACD) of skin of that individual's foot or toes.

Repeatability

The repeatability of this method of measuring ACD has been tested in a separate study[6]. The measurement of ACD was performed on two separate occasions, at intervals varying from 1 to 18 days, in ten subjects. The mean agreement rate ((100 – (difference between the two measurements/mean of the two measurements) × 100) per cent) was 93·5 per cent and the correlation coefficient between the pairs of measurements was 0·97 ($P < 0·001$).

Statistical analysis

Individual values of ACD were normally distributed in all three groups and the mean, standard deviation and standard error of sample mean for each group were calculated accordingly. The t distribution was used to measure confidence intervals and standard error of mean, and analysis of co-variance was used to assess the significance of differences in mean capillary density between the three groups by adjusting for differences in age and sex between the groups. Student's t test was used to assess the significance of the correlation coefficient between capillary density and other variables. The paired t test was used to assess the significance of differences in capillary density values between right and left sides in each group.

Results

Average capillary density

Individual values of ACD for the foot and toes of each subject in all three groups are shown in *Figs 2* and *3* respectively.

In group 1 (n = 19), mean(s.e.m.) (range) ACD values of right and left sides were 33·7(1·9) (19–56) and 34·4(1·7) (16–48) per mm^2 respectively in the foot, and 49·7(2·3) (26–61) and 45·1(2·6) (27–62) per mm^2 respectively in the toes.

In group 2 (n = 21), ACD values of symptomatic and contralateral sides were 31·2(1·8) (19–47) per mm^2 (P not significant) and 31·9(2·6) (12–53) per mm^2 (P not significant) respectively in the foot, and 46·5(2·4) (30–65) per mm^2 (P not significant) and 42·8(2·1) (33–59) per mm^2 (P not significant) respectively in the toes.

In group 3 (n = 23), ACD values of symptomatic and contralateral sides were 22·0(1·8) (9–47) per mm^2 ($P < 0·001$) and 24·3(1·7) (10–42) per mm^2 ($P < 0·001$)

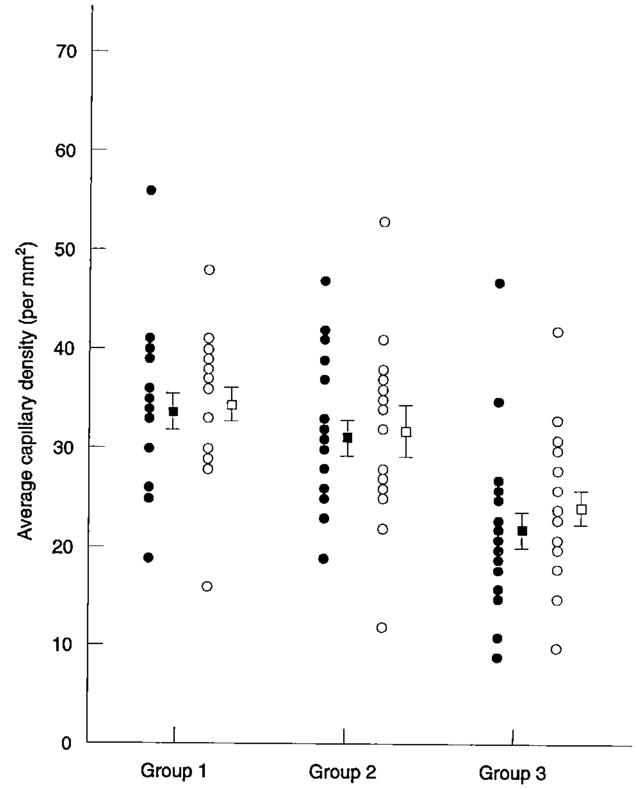

Fig. 2 Individual values of foot average capillary density in right (●) and left (○) sides of subjects in group 1, and in symptomatic (●) and contralateral (○) sides of patients in groups 2 and 3. Boxes and bars are mean(s.e.m.) values

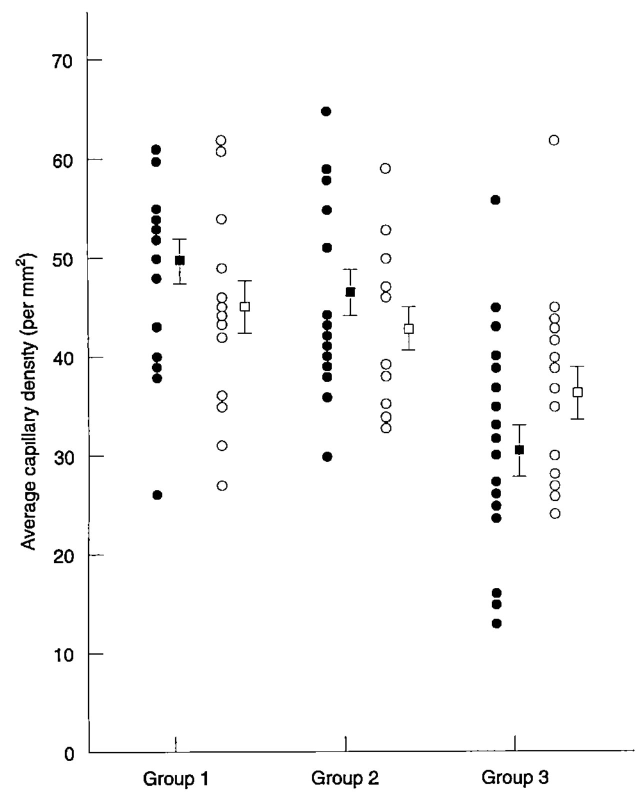

Fig. 3 Individual values of toe average capillary density in right (●) and left (○) sides of subjects in group 1, and in symptomatic (●) and contralateral (○) sides of patients in groups 2 and 3. Boxes and bars are mean(s.e.m.) values

respectively in the foot, and 30·6(2·4) (13–56) per mm^2 ($P < 0·001$) and 36·4(2·7) (24–62) per mm^2 ($P < 0·001$) respectively in the toes.

After adjusting for age, sex and ABPI, using analysis of co-variance, mean ACD of the foot and toes, both of symptomatic and contralateral sides, was significantly lower in group 3 ($P < 0·001$) than in groups 1 and 2, but there was no significant difference between mean ACD of groups 1 and 2.

The characteristics of subjects (in all three groups) with an ACD in the lowest quartile of that group were compared with those of the group as a whole. There were no significant differences in age, sex and ABPI between the subgroups and their respective groups (*Table 1*).

Comparison between right and left sides

The relationship between individual values of ACD between right and left sides in group 1, and symptomatic and contralateral sides in groups 2 and 3 was compared. The correlation coefficients were 0·89 ($t = 8·05$, 17 d.f., $P < 0·001$), 0·84 ($t = 6·75$, 19 d.f., $P < 0·001$) and 0·70 ($t = 4·49$, 21 d.f., $P < 0·001$) for groups 1–3 respectively.

Relation of average capillary density to age and other variables

The relationship of capillary density to age in all subjects was examined. The change in capillary density per year of age was – 0·155 capillaries/year (*Fig. 4*). The relationship of capillary density to ABPI in the feet of subjects from all three groups is shown in *Fig. 5*.

The significance values of any relationship of capillary density to age, sex, smoking, diabetes and ABPI are summarized in *Table 2*.

In group 3, mean ACD was significantly lower ($P < 0·001$) in the subgroup of patients with ulceration ($n = 19$) than in the subgroup with rest pain but no ulceration ($n = 4$) (*Table 3*).

Table 1 Characteristics of subjects with average capillary density in the lowest quartile compared with the group as a whole

Group	No. of subjects	Mean ACD (per mm^2)	Mean age (years)	Sex ratio (M : F)	No of smokers	No of diabetics	Mean ABPI*
Group 1							
Lowest quartile	5	25·7	65	2 : 3	2	1	0·86
Whole group	19	34·1	67	12 : 7	6	1	0·90
Group 2							
Lowest quartile	5	23·4	72	5 : 0	0	2	0·65
Whole group	21	31·2	68	19 : 2	5	5	0·55
Group 3							
Lowest quartile	6	14·7	78	3 : 3	1	1	0·28
Whole group	23	22·0	76	15 : 8	5	6	0·28

*In group 1, this is the mean of right and left sides. In groups 2 and 3, this refers to the symptomatic side. ACD, average capillary density, ABPI, ankle brachial pressure index

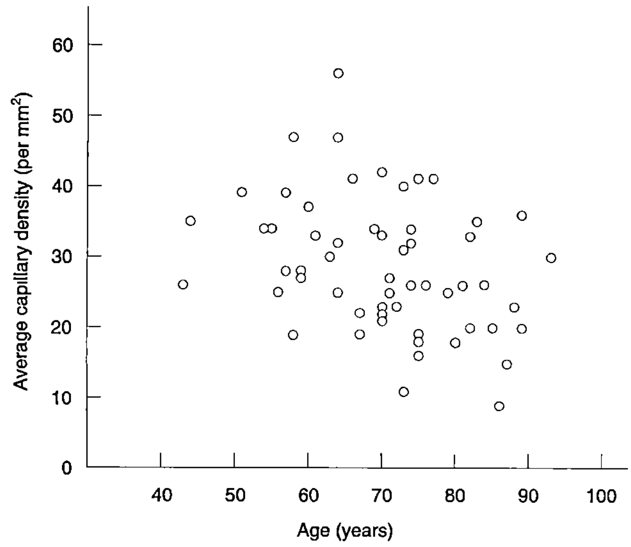

Fig. 4 Relationship between average capillary density and age in all subjects

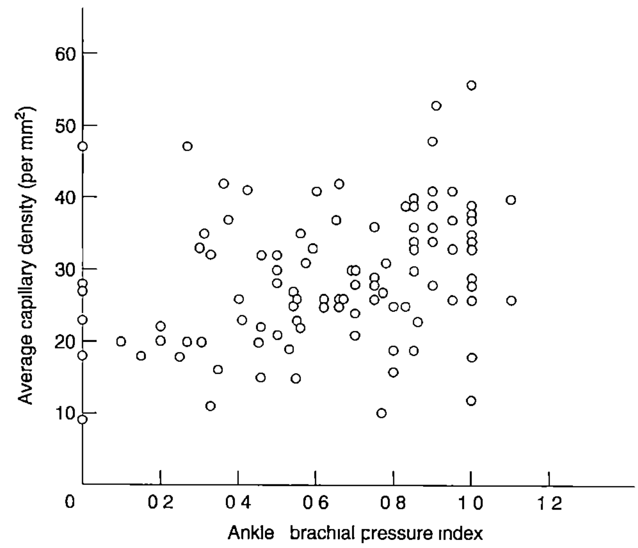

Fig. 5 Relationship between average capillary density and ankle: brachial pressure index on both sides in all subjects

Table 2 Relationship of foot average capillary density to other variables

	Group 1	Group 2	Group 3
Age (correlation coefficient)	−0·08	−0·31	−0·37
Sex (mean ACD; per mm^2)			
Men	34·0 (n = 12)	31·3 (n = 19)	23·4 (n = 15)
Women	34·2 (n = 7)	36·0 (n = 2)	21·1 (n = 8)
Smoking (mean ACD; per mm^2)			
Non-smokers	35·0 (n = 13)	30·9 (n = 16)	23·5 (n = 18)
Smokers	31·5 (n = 6)	34·0 (n = 5)	20·2 (n = 5)
Diabetes (mean ACD, per mm^2)			
Non-diabetic	34·5 (n = 18)	32·0 (n = 16)	22·5 (n = 17)
Diabetic	27·0 (n = 1)	31·1 (n = 5)	22·9 (n = 6)
ABPI (correlation coefficient)			
Symptomatic side*	0·51‡	−0·28	−0·05
Contralateral side†	0·45‡	−0·05	−0·27

*Right side in group 1; †left side in group 1 ACD, average capillary density, ABPI, ankle : brachial pressure index. (P < 0·05)

Table 3 Comparison of average capillary density in subgroups of patients with rest pain only and patients with ulceration with or without rest pain

	Average capillary density (per mm^2)	
	Rest pain only (n = 4)	Ulceration ± rest pain (n = 19)
Foot		
Symptomatic side	30·5	19·9*
Mean of both sides	30·5	20·9*
Toes		
Symptomatic side	44·3	27·4*
Mean of both sides	44·8	29·0*

*P < 0·001 (Student's t test)

Discussion

The most important finding in this study was the significantly lower anatomical capillary density (i.e. total number of capillaries per unit area) in patients with ischaemic ulceration, compared with patients with claudication and control subjects. A reduced capillary density in patients with severe limb ischaemia has been reported previously[8,9]. Earlier studies have based their conclusions on essentially qualitative observations of reduced capillary numbers in the skin of the foot immediately adjoining an ischaemic ulcer. In the present study a technique was used that addressed the methodological problem of spatial variation of capillary density and quantitatively measured

ACD of the skin of the whole of the foot and toes. Furthermore, in this study, capillary density was measured in the contralateral foot of all subjects. This was found to parallel that of the symptomatic foot and to be independent of ABPI.

Patients in group 3 were on average older than those in groups 1 and 2, but it is unlikely that age would account for the significantly reduced ACD in group 3, as there was no significant correlation between age and ACD. Even after correcting for age, ACD was still significantly lower in group 3 than in the other groups. The reduced anatomical capillary density in group 3 may be attributed to a significantly reduced arterial inflow pressure (mean ABPI in the symptomatic side 0·28 compared with 0·55 and 0·90 in claudicants and controls respectively). Reduced macrocirculatory blood flow in these patients might lead to a reduction in the total number of capillaries in the skin of the foot, whatever the mechanism and time span of this process. There was, however, no significant correlation between ACD and APBI in the symptomatic leg of subjects in groups 2 and 3. Indeed some patients with a very low ABPI had a higher ACD than the mean for that group. Further evidence against a direct relationship between blood flow and capillary density was obtained by comparing right and left sides. Were blood flow to have a direct influence on anatomical capillary density, ACD would be expected to be lower in the symptomatic than in the contralateral leg. The present results refuted this. First, mean ACD of symptomatic and contralateral sides in groups 2 and 3 were similar in spite of significantly different mean values of ABPI. Second, comparison of individual ACD in symptomatic with contralateral sides in each patient showed significant positive correlation despite marked differences between the ABPI on each side. Similar results were also found when comparing right and left sides in control subjects.

In the light of this, it is suggested that anatomical capillary density in the skin of the foot of an individual might be an intrinsic constitutional property of that individual, normally distributed in the population, and independent, at least in part, of haemodynamic parameters. Genetic factors might play a central role in determining capillary geometry in the skin: it is well accepted in the embryological literature that the establishment of blood vessels may be genetically predetermined and that they arise independently as angioblasts at several sites within the embryo[10]. Hereditary factors remain significant in vessel formation for a surprisingly long time. It is known for instance that establishment of vascular patterns continues for substantial periods even after the heart has been excised[11,12]. Similar genetic factors might operate on the cutaneous microvasculature in humans.

The effect of reduced skin capillary density on tissue nutrition remains unknown. Cross-sectional capillary density in tissue is considered to be one of the determinant factors of tissue oxygenation. It is natural to assume that an area of skin with fewer capillaries per unit area will have a lower average oxygen tension. This is supported by experimental as well as theoretical work. Theoretically, various models have been formulated to study the relationship of capillary density to optimal oxygen delivery[13–16]. Small differences in capillarity and hence intercapillary distances have been shown to produce profound changes in oxygen tension in the myocardium[17], and tissue oxygen tension has been shown to vary in proportion to capillary density (although not always in linear fashion). Most of these models apply to microcirculatory behaviour in skeletal muscle and an element of uncertainty is therefore inevitable when extrapolating these findings to skin. Notwithstanding this, experimental verification of such theoretical considerations has become possible owing to the development of a transparent transcutaneous oxygen electrode which permits simultaneous measurement of the oxygen tension of the skin ($TcpO_2$) and examination of the nutritional capillaries of the skin by video microscopy[18]. Using this technique, Franzeck *et al.*[19] have studied the relationship between oxygen tension and capillary density in patients with chronic venous insufficiency; although there was not a direct correlation between the number of capillaries per square millimetre and $TcpO_2$, $TcpO_2$ levels seemed to depend on capillary density. Reduced $TcpO_2$ values were found in regions with decreased capillary density and very low values in areas without capillaries. Reduced capillary density leads to local hypoxia and it is possible that an intrinsically low capillary density in group 3 patients may play a central role in the pathophysiology of skin ulceration.

As ACD was found to be normally distributed in the population of each group, patients in the lower range of the normal distribution of ACD might be more prone to developing skin ulceration, and those with an intrinsically higher ACD may 'escape' ulceration in spite of severe arterial disease. This was indeed found to be the case: mean values of ACD in the subgroup of group 3 patients who had rest pain only and no ulceration (mean ABPI 0·35) were 30·5 and 44·8 per mm^2 for the foot and toes respectively, compared with 20·9 and 29·0 per mm^2 for foot and toes respectively (mean ABPI 0·25) in the subgroup with ulceration, although overall numbers were small.

The relationship between an individual's ACD and the success of revascularization may have important clinical implications. Improvement of claudication is mostly a function of the success of revascularization of the affected muscle. It has therefore been assumed that partial or complete resolution of ischaemic foot ulcers similarly depends on the success of revascularization of the tissues. This assumption takes no consideration of any inherent microcirculatory abnormality in the affected subject. In this respect, it is significant that patients in group 3, whose ACD lay at the lower extreme of the range, had no improvement in their ulcers despite haemodynamically successful revascularization. Further studies specifically examining the relationship between ACD and the clinical response to revascularization are needed.

Acknowledgements

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Original article

Primary myocutaneous flap closure following resection of locally advanced pelvic malignancies

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Background: Perineal wounds, created at the time of extended resection for locally advanced malignancy and following chemoradiation, are at risk of serious complications.

Methods: To determine whether immediate myocutaneous flap closure prevents complications, 57 patients treated with multimodality therapy and proctectomy (35 perineal wounds) or sacrectomy (22 posterior wounds) were studied. Patients were categorized according to whether they underwent primary skin and pelvic closure (group 1; $n = 20$); primary skin and omental pelvic closure (group 2; $n = 24$); or immediate myocutaneous flap closure (group 3; $n = 13$).

Results: Groups were similar with respect to age and sex; however, group 1 had more primary tumours and required less radical surgery and chemoirradiation than groups 2 and 3. Groups 1 and 2 experienced more complications overall (eight of 20, nine of 24 and three of 13 patients in groups 1, 2 and 3 respectively), more acute wound complications (seven of 20, nine of 24 and two of 13), delayed wound healing (three of 20, six of 24 and one of 13) and more reoperations for perineal wound problems (five of 20, seven of 24 and zero of 13). Patients in group 2 had a significantly longer hospital stay than those in group 1. Flap closure (group 3) did not increase the length of stay. The routine use of primary flap closure reduced overall wound complications (eight of 31 *versus* ten of 26 patients) and length of hospitalization (13 *versus* 17 days).

Conclusion: Complete wound healing was achieved in all patients; however, immediate myocutaneous flap closure reduced the need for readmission and reoperation.

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Introduction

Results of recent studies from this[1,2] and other[3] institutions demonstrate that locally advanced and recurrent anorectal malignancies can be treated successfully with a multimodal approach using preoperative external beam irradiation with concomitant chemotherapy, followed by aggressive surgery and intraoperative electron beam radiation therapy (IOERT). Five-year survival rates as high as 46 per cent in patients with locally advanced (T_4) primary cancers[4] and 34 per cent in patients with locally recurrent rectal cancers[5] can be accomplished. Unfortunately, to achieve local control often necessitates extensive pelvic surgery in irradiated tissues with the attendant risk of acute and chronic complications.

Approximately half of all patients presenting with recurrent pelvic malignancy after low anterior resection or abdominoperineal resection will require an extensive pelvic procedure, typically including resection of residual rectum, sacrum, uterus, vagina, bladder, hypogastric vessels or large areas of soft tissue[5–7]. Although mortality rates can be as low as 0 per cent[6,8], morbidity rates are reported to range from 25 to 60 per cent[6,8–10]. For procedures requiring a posterior wound, such as sacrectomy, the risk of serious wound complications can be as high as 25–46 per cent[6,8,9]. Having recognized difficulties associated with posterior and perineal wounds following multimodality therapy, the authors have adopted a practice of more routine application of primary myocutaneous flap closure for patients undergoing multimodality therapy and aggressive pelvic surgery with resulting large pelvic defects[11]. Results of this practice are reported.

Patients and methods

Between January 1990 and June 1996, 95 patients of a single surgical practice underwent pelvic resection for locally advanced primary or locally recurrent anorectal cancer. Fifty-seven patients had either a perineal ($n = 35$) or posterior ($n = 22$) wound and were the subject of this study. Patients were categorized according to whether they underwent primary skin and pelvic closure (group 1; $n = 20$); primary skin closure with a pedicle omental graft for pelvic closure (group 2; $n = 24$); or immediate myocutaneous flap closure (group 3; $n = 13$). Patient charts were reviewed to establish operative and cancer details including preoperative and intraoperative therapies and details of postoperative recovery.

The more routine use of primary myocutaneous flap closure was introduced in the last 3 years of the study in an attempt to reduce rates of wound complications. From 1990 to 1993 there were substantially more patients in groups 1 (eight of 26 patients) and 2 (16 of 26) than in group 3 (two of 26). From 1994 to 1996 there were more patients in groups 1 (12 of 31 patients) and 3 (11 of 31) than in group 2 (eight of 31). Between the two time periods, the use of primary closure (group 1) remained essentially the same: eight procedures were performed up to 1993 and 12 after 1994. However, use of the omental pedicle flap declined from 16 operations before to eight after 1994; use of the primary myocutaneous flap increased from two procedures before to 11 after 1994.

In group 1, after primary closure of the perineum and closure of the pelvic peritoneum, two suction drains were placed into the presacral space, pulled through the floor of the ischiorectal fossa on either side of the perineal wound and placed under low suction for at least 5 days or when the volume of fluid collected was less than 30 ml/day for each drain. In group 2, after primary closure of the perineum, the presacral space was obliterated with an omental pedicle flap. This was created by release of the greater omentum from the stomach by ligation of the branches of the gastroepiploic arcade and transfer of this tissue to the pelvic cavity[12]. In group 3, a rectus abdominis myocutaneous flap was constructed by release of the rectus muscle from the costal margin, followed by dissection of the muscle away from the anterior rectus sheath, and placement within the pelvis (*Fig. 1*). The blood supply to the rectus abdominis muscle flap was based on the inferior epigastric artery[11,13].

Results

Patients details

Patients in groups 1, 2, and 3 were similar with respect to mean age and sex (58, 59, and 57 years; M : F ratio 13 : 7, 17 : 7 and 8 : 5 respectively). There tended to be more primary cancers in group 1 (seven of 20), and more recurrent cancers in groups 2 (21 of 24) and 3 (ten of 13). Thirteen patients had primary lesions and 44 patients had recurrent malignancies. Tumours included rectal adenocarcinoma ($n = 50$), squamous cell carcinoma of the anus ($n = 3$), pelvic chordoma ($n = 2$) and cloacogenic carcinoma ($n = 2$). For the 44 patients with recurrent rectal cancer, this was the first recurrence in 39 and the second recurrence in five. Thirty-one recurrences were symptomatic with either pain ($n = 29$) or persistent sinus ($n = 2$). The remainder were detected by computed axial tomography.

Previous therapy

Forty-four patients had undergone at least one previous operation including low anterior resection in 20; abdominoperineal resection for the primary cancer in 16 patients and for treatment of the first recurrence in four; and a trans-sacral ($n = 2$), Hartmann's ($n = 1$) or other ($n = 1$) procedure. Twenty-one of the 44 patients with recurrent cancer had received adjuvant irradiation or chemotherapy for management of the primary tumour before this presentation. Three of the five patients with a second recurrence were treated with external irradiation at the time of the first recurrence. Twenty-five patients also received adjuvant chemotherapy to manage the initial tumour or for treatment of the first recurrence.

Preoperative therapy

All 57 patients received external beam radiation therapy just before or following the current surgery, either as neoadjuvant (13 patients) or as preoperative or postoperative treatment of a first or second recurrence. The dose of external beam radiation delivered ranged from 45 to 55 Gy in previously unirradiated patients and from 10 to 30 Gy in previously irradiated patients. The extent of disease necessitated IOERT in 49 patients (86 per cent; dose range 10–20 Gy), and placement of brachytherapy catheters in one patient that was loaded 6 days after operation.

Operative details and postoperative results

In patients with no evidence of distant metastasis at laparotomy, abdominoperineal resection with or without pelvic exenteration, or sacrectomy was performed using a combined abdominal and perineal or posterior approach (*Table 1*). Patients in group 1 were more likely to undergo abdominoperineal resection than sacrectomy or pelvic exenteration. Mean operative times were longer for groups

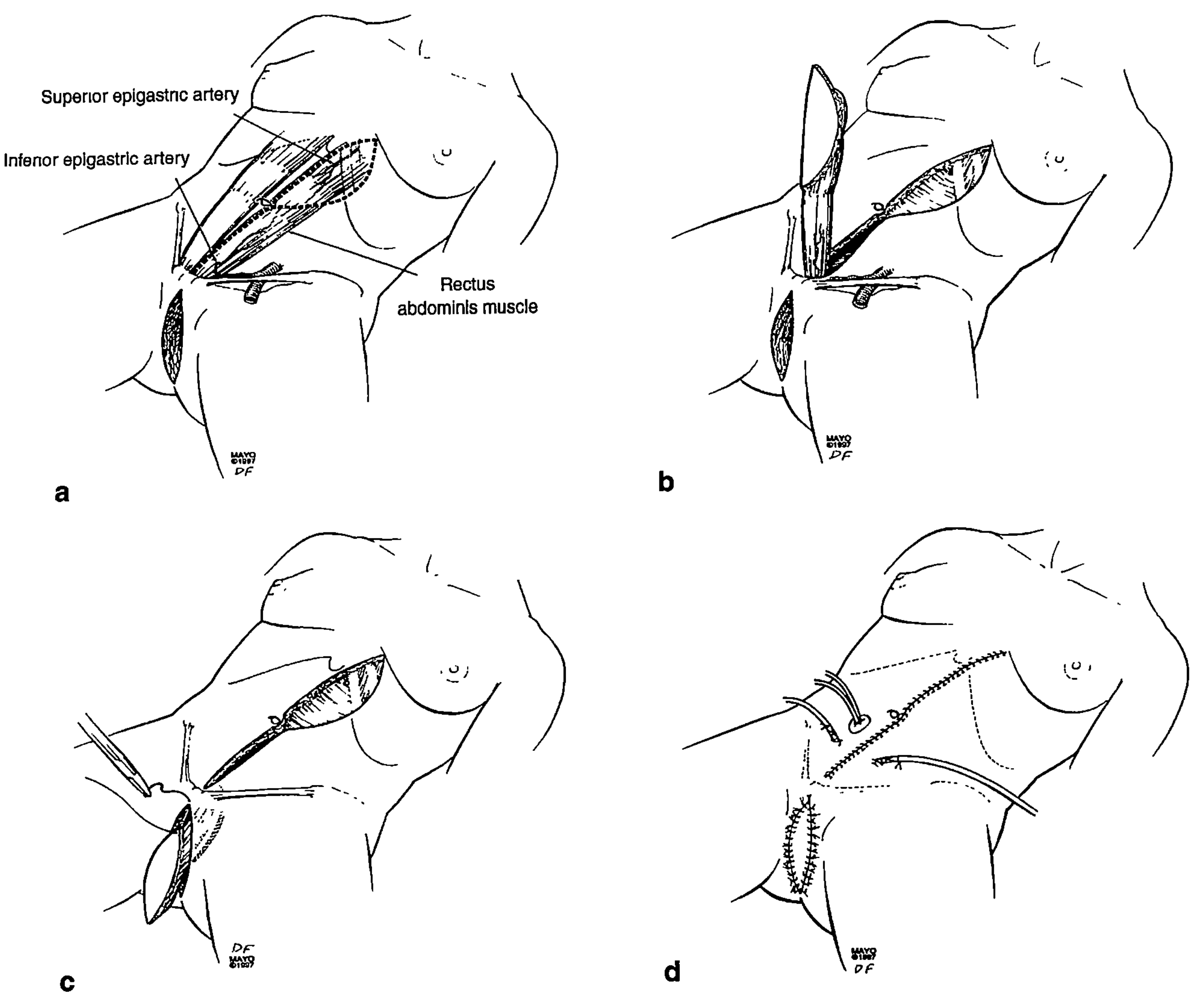

Fig. 1 **a** Once perineal resection is complete, the skin paddle is designed to match the size of the defect. The harvest site for the skin paddle is determined based on the direct perforators from the underlying rectus abdominis muscle. **b** The myocutaneous flap and associated skin paddle is raised and includes the anterior fascia of the rectus sheath. The blood supply is provided by the inferior epigastric artery. **c** The flap is delivered through the pelvis to the perineal defect. Care is taken to avoid stretch or torsion on the inferior epigastric blood supply **d** The skin paddle is secured with interrupted sutures, and the abdominal fascia and skin are reapproximated. Reproduced with permission from the Mayo Clinic, Rochester, Minnesota, USA

2 and 3 than for group 1 (*Table 2*). Differences between groups 2 and 3 were not marked, suggesting that the extent of resection rather than the flap itself accounts for the increased times. The mean operative blood loss was similar for each group. For the initial hospitalization, patients in group 2 stayed longer than those in group 1. When readmissions for wound problems were included, the mean total stay for group 2 was much longer than that for group 1.

Table 1 Current surgical procedures

	Group 1 (n = 20)	Group 2 (n = 24)	Group 3 (n = 13)
APR	12 (60)	7 (29)	3 (23)
APR and sacrectomy	3 (15)	9 (38)	4 (31)
Pelvic exenteration	3 (15)	3 (13)	5 (38)
Pelvic exenteration and sacrectomy	1 (5)	4 (17)	0 (0)
Other*	1 (5)	1 (4)	1 (8)

Values in parentheses are percentages. *Perineal excision, sacrectomy alone and small bowel resection (one each) APR, abdominoperineal resection

Table 2 Operative and postoperative results

	Group 1	Group 2	Group 3
Operating time (h)*	7(2) (4–16)	10(3) (5–11)	11(2) (7–14)
Blood loss (units)	5 (0–38)	5 (0–23)	7 (0–24)
First hospital stay (days)†	12 5 (8–30)	17 2 (9–39)	15 2 (10–31)
No. of readmissions‡	4	7	2
Second hospital stay (days)‡	21 3 (9–45)	10 3 (2–17)	6 5 (6–7)
Total hospital stay (days)	15 3 (8–64)	20 7 (9–51)	16 1 (10–37)

Values are mean (range) or *mean(s d) (range) †For initial surgery; ‡specifically for wound management

Postoperative complications and deaths

There were no perioperative deaths, and no perioperative complications in the abdominal wounds of these patients. Acute (30-day) perioperative complications were more common in groups 1 and 2 than in group 3 (*Table 3*). There was a consistent trend toward more acute wound problems (infection or dehiscence) requiring readmission and reoperation in group 2. The incidence of wound complications was higher in the period 1990–1993 (ten of 26 patients) before routine use of the vascularized myocutaneous flap in the period 1994–1996 (eight of 31 patients). Similarly, the initial and total lengths of hospital stay were greater before routine use of the flap (from 1990 to 1993; 17 and 20 days respectively) than after the introduction of routine use of the flap (between 1994 and 1996; 13 and 17 days respectively).

Long-term results, complications and deaths

Overall acute and/or chronic complications, including small bowel obstruction, ureteral obstruction and other problems not related to the wound, occurred in 14 of 20 patients in group 1, 19 of 24 in group 2 and nine of 13 in group 3. Chronic wound complications included one case of persistent perineal sinus at the border of a myocutaneous flap in a patient in group 3, which was treated conservatively without surgery. In addition, there were two cases of persistent perineal sinus in group 2; one was treated by distal sacrectomy with good result and the second was treated by debridement with curettage.

Table 3 Postoperative complications*

	Group 1 (*n* = 20)	Group 2 (*n* = 24)	Group 3 (*n* = 13)
Overall morbidity†	8 (40)	9 (37)	3 (23)
Acute wound complications	7 (35)	9 (37)	2 (15)
Delayed wound healing	3 (15)	6 (25)	1 (8)
Readmission, perineal wound	4 (20)	7 (29)	2 (15)
Reoperation, perineal wound	5 (25)	7 (29)	0 (0)
Delayed conversion to flap	3 (15)	5 (21)	0 (0)

Values in parentheses are percentages *At posterior and perineal surgical sites only †Overall acute complications within 30 days after operation

Discussion

An aggressive multimodal approach to pelvic malignancy is increasingly preferred both for the possibility of cure and for palliative management of disabling pelvic conditions. In this series, locoregional disease was often technically difficult to access, involved multiple structures, and often required extensive resection to accomplish negative margins. Although resections could be achieved with acceptable morbidity, 35 per cent of these patients experienced significant postoperative morbidity. These results are in keeping with previously published morbidity rates of between 25 and 60 per cent[8,10]. Although the relative contribution of preoperative external beam irradiation and IOERT to the risk of complications cannot be determined, it has previously been reported that patients treated with the latter and more aggressive surgery are at an increased risk of complications[5]. Regardless of whether they are due to the effects of chemoradiation or problems with residual dead space, perineal and posterior wounds can unfortunately be the source of undesirable morbidity and the cause of prolonged hospital stay[16,17].

In response to wound healing complications, two general approaches to wound management have been practised. The first employs primary perineal wound closure with or without an omental pedicle graft for pelvic space obliteration followed by delayed myocutaneous flap advancement as required for wound complications[17,18]. Primary wound closure without flaps is technically straightforward and expeditious; however, in the event of complications and wound breakdown the risk of chronic failure due to pelvic sepsis[12] and fibrosis can jeopardize the ultimate success of pelvic closure and wound healing. The second practice makes use of primary myocutaneous flap advancement for all perineal wounds[17]. Primary myocutaneous grafting is technically more demanding but adequate wound coverage with non-irradiated vascularized tissue is achieved in a single procedure.

In response to a high rate of perineal and posterior wound complications (ten of 26 patients) early in this experience (1990–1993), the authors' practice was modified to include the use of primary myocutaneous flaps principally for large fibrotic pelvic defects. Although the series is too small to confidently support rigorous statistical power when comparing the two time periods or the different treatment groups, several conclusions can still be drawn.

First, after the introduction of selective application of primary flaps, the overall rate of wound complications decreased from 38 per cent (ten of 26 patients) to 26 per cent (eight of 31). Second, patients treated with the flap (group 3), despite undergoing more extensive resection for recurrence than those without flap closure (group 1), had fewer complications overall, fewer acute and delayed wound complications, and required fewer readmissions and reoperations. The same was true for the omental closure group *versus* the myocutaneous flap group with respect to fewer serious complications, even though these groups were similar with respect to extent of resection and previous therapies. No doubt when the transition was made to use of primary myocutaneous flaps, this was most often applied to patients who would otherwise have undergone at least an omental closure. This is supported by the fact that the proportion of patients in group 2 declined as the proportion in group 3 increased after 1993.

It was anticipated that the use of primary myocutaneous flaps would increase operating times and primary length of hospital stay. Surprisingly, operation times were not influenced greatly by the use of the flap. That operations in groups 2 and 3 took longer than those in group 1 is best explained by the fact that more extensive procedures were required, and that more of these patients underwent reoperation for recurrent disease. In fact, the difference in mean operating time between the omental and myocutaneous flap groups was only 1 h. Regarding length of stay for the index procedure, patients in group 3 tended to stay longer than those in group 1, although this difference was not noted when readmissions for wound complications were used to calculate a total length of stay. Since groups 2 and 3 were most comparable in terms of procedures, it is relevant to note that myocutaneous flap construction did not increase the length of initial or overall hospital stay.

In summary, the more routine use of myocutaneous flaps was associated with a reduction in serious wound complications without a significant increase in operating times or length of stay. Thus, there appears to be no obvious drawback to the primary application of myocutaneous flaps for closure of large perineal or posterior wounds in patients treated with multimodality therapies including extended resection. What remains unanswered is whether the indications for primary flap closure should be widened. Results from this study suggest there could be further gains if the flap was applied in some locally advanced primary rectal cancer cases as done for three patients in the present series. Although it is not advised for all cases of primary rectal cancer, as further prospective assessments should be performed first, it seems reasonable to recommend the use of the flap for locally advanced rectal cancers requiring intense preoperative and intraoperative chemoradiation. The size of the pelvic defect, presence of fibrosis, condition of the perineal or posterior skin, and the availability of alternative sources of vascularized tissue (omentum) should influence the decision to use the flap at the first operation for rectal cancer.

Application of a primary rectus abdominis myocutaneous flap at the time of surgery represents an effective means of closing large pelvic defects and providing healthy vascularized non-irradiated skin to heavily radiated wounds. In patients in whom perineal wound failure has occurred after attempted primary wound approximation, delayed myocutaneous flap closure represents an important means of achieving wound healing.

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Original article

Identification of patients likely to benefit from biofeedback for outlet obstruction constipation

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Background: Biofeedback for outlet obstruction constipation has a varying success rate. The aim of this study was to identify which patients are likely to respond to biofeedback.

Methods: Thirty patients with severe outlet obstruction constipation were treated by a specialist nurse using three or four sessions of visual and auditory feedback of anal sphincter pressures. All patients were assessed by evacuating proctography, whole-gut transit studies and anorectal physiology before treatment.

Results: Two patients did not complete the course of biofeedback. Nine patients improved. Before treatment these patients had predominantly normal anorectal physiology and were all able to open the anorectal angle at evacuating proctography. Nineteen patients did not improve, of whom only three had no measured abnormality other than inability to empty the rectum. Ten of these patients had abnormal anorectal physiology which may have been due to previous vaginal delivery.

Conclusion: Biofeedback for outlet obstruction constipation is more likely to be successful in patients without evidence of severe pelvic floor damage.

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Introduction

The concept that constipation might be due to pelvic floor abnormality was first mooted in the mid-1980s[1]. Since then the terms 'outlet obstruction constipation' and 'anismus' have become associated with this problem. Patients complain of difficulty in rectal emptying, excessive straining at stool and often report digitation to aid evacuation. Despite considerable research, the aetiology of outlet obstruction constipation remains poorly understood.

Investigation of defaecation is difficult because of the artificial situation created by the investigation. The original finding was that some patients with constipation could not expel a balloon from the rectum[1]. Anorectal physiology shows increased sphincter pressure and electromyographic recruitment on attempts to defaecate[1]. On evacuating proctography patients may fail to open the anorectal angle[2], contract rather than relax the puborectalis (puborectalis paradox)[3] or may be unable or slow to evacuate contrast[4]. Many findings initially reported to be abnormal and associated with outlet obstruction constipation have been found in asymptomatic controls[5–7]. Anatomical abnormalities such as rectocele, intussusception and anterior mucosal prolapse may also be seen in these patients, but it is difficult to know whether the anatomical abnormality is the cause or the effect of the functional problem. Nevertheless there appears to be a group of patients who have difficulty in evacuation of stool, whether due to ineffectual evacuation, lack of pelvic floor relaxation or ballooning of the pelvic floor. The term outlet obstruction constipation has been applied to these patients.

Surgical treatment of outlet obstruction constipation has included division of the puborectalis muscle[8] and anorectal myectomy[9,10]. These treatments were not effective and carry a risk of incontinence. Biofeedback therapy, providing visual and/or auditory feedback of the activity of the pelvic floor muscles, was initially hailed as very successful in this condition[11,12] but recent reports are less optimistic[13,14]. This study examined the results of biofeedback in a consecutive group of 30 patients with outlet obstruction constipation to determine whether a subgroup of patients who may benefit can be identified.

Patients and methods

Biofeedback was used in 30 female patients with severe symptoms of outlet obstruction constipation.

Entry criteria

All patients had severe constipation with failure to respond to laxative treatment and enemas. No patient was able to empty more than 20 ml of contrast at evacuating proctography and all were unable to expel a rectal balloon during anorectal physiological testing. No patient had a large rectocele or an intussusception.

Before treatment all patients underwent barium enema and/or colonoscopy to exclude stricture, megarectum or other serious pathology, and had biochemical screening to exclude metabolic disorders such as diabetes, hypothyroidism and hypercalcaemia.

Investigations

Whole-gut transit studies[15] and evacuating proctography were performed followed by anorectal physiological tests. Maximum resting and squeeze pressures (MRP and MSP respectively) and sphincter length were measured by a combination of rapid pull-through (MRP, sphincter length) and station pull-through (MSP) techniques using a microtransducer (Gaeltec, Isle of Skye, UK) with a computerized analysis system (Albyn Medical, Dingwall, UK). All patients had the anorectal inhibitory reflex elicited. Sensation of rectal filling was measured using a steady fill rate of 25 ml/min with normal saline and recording the volume of first sensation, first desire to defaecate and maximum tolerated volume. Pudendal nerve terminal motor latency was also measured (Dantec Neuromatic 2000; Skovlunde, Denmark).

The patients were reviewed at the outpatient clinic by a specialist colorectal surgeon who explained the nature of the functional pelvic floor problem to them.

Biofeedback method

Biofeedback therapy comprised three or four outpatient biofeedback sessions using visual and auditory feedback of sphincter pressures during attempts to relax the pelvic floor and expel a rectal balloon. The treatment was performed by a specialist nurse. Standard anorectal physiology equipment was used for this purpose. The session included an explanation of the basic anatomy of the pelvic floor and the mechanism of defaecation, and all patients were given a pelvic floor exercise sheet. The first biofeedback session lasted a total of 90 min and each subsequent appointment 60 min.

All patients were subsequently reassessed at the outpatient clinic and any change in symptoms was recorded together with the patient's estimation of whether symptoms had improved.

Characteristics of patients who showed improvement or no improvement were compared using Mann–Whitney tests, taking $P < 0{\cdot}05$ to be significant. The significance of normal investigations in predicting improvement after biofeedback was compared using the χ^2 test.

Results

Patient characteristics

All 30 patients were female. The median age was 35 (range 15–55) years. Eighteen patients had previous vaginal deliveries (range 1–3) and three patients dated their symptoms from childbirth. Five had undergone haemorrhoidectomy and seven hysterectomy in the past. Two patients had previous total colectomy and ileorectal anastomosis. Fifteen patients had received treatment for psychological disorders ranging from short-term anxiolytic to long-term antidepressant therapy.

A pretreatment evacuating proctogram showed that no patient had a rectal intussusception or large rectocele (greater than 2 cm). *Table 1* lists the details of the physiological tests.

Outcome

Two patients did not complete the programme because of anal discomfort.

In nine patients symptoms were improved after biofeedback. They all became able to expel a rectal balloon and were able to reduce the anal sphincter pressure on straining down. Before commencing biofeedback these patients had predominantly normal anorectal physiology and all could open the anorectal angle at evacuating proctography (*Tables 2* and *3*).

Nineteen patients did not improve after biofeedback. Three patients were able to expel a balloon in the laboratory but continued to complain of symptoms. The other 16 were characterized by continuing inability to expel a

Table 1 Characteristics of 30 patients with outlet obstruction constipation

Maximum resting pressure (mmHg)*	61 (24–98)
Maximum squeeze pressure (mmHg)*	102 (33–282)
First sensation (ml saline)*	27 (5–226)
Median PNTML < 2·3 ms	12 of 14
Anorectal angle opens	23
Very slow transit (> 50% markers present at 10 days)	6
Slow transit (> 20% markers present at 5 days)	17

*Values are median (range) PNTML, pudendal nerve terminal motor latency

Table 2 Patient characteristics before biofeedback

	Improved	Not improved	P†
No. of patients	9	19	
Maximum resting pressure (mmHg)*	73 (24–98)	55 (27–93)	< 0·03
Maximum squeeze pressure (mmHg)*	121 (63–282)	78 (33–156)	< 0·03
First sensation (ml saline)*	30 (5–152)	53 (10–226)	
Anorectal angle opens	9	13	
Slow transit (> 20% markers present at 5 days)	5	12	
Very slow transit (> 50% markers present at 10 days)	2	4	
Psychiatric problems	6	7	

*Values are median (range) The two patients who did not complete biofeedback are not included †Mann–Whitney test

Table 3 Patient characteristics before biofeedback treatment as predictors of success

	Normal	Abnormal	P*
Maximum resting pressure > 50 mmHg	8 of 20	1 of 8	0·16
Maximum squeeze pressure > 100 mmHg	8 of 16	1 of 12	0·02
First sensation < 70 ml saline	7 of 20	1 of 7	0·3
Anorectal angle opening	9 of 22	0 of 6	0·05
Gut transit < 20% markers 5 days	4 of 11	5 of 17	0·7
Psychiatric history	3 of 15	6 of 13	0·14

The number of patients who were successful with biofeedback compared with the total for each group is shown for each characteristic Two patients who did not complete biofeedback because of anal discomfort are not included $^*\chi^2$ test

rectal balloon and a rise in anal sphincter pressure on straining down. In contrast to those in the 'improved' group, only three of these patients had no measured abnormality on pretreatment anorectal physiology or evacuating proctography apart from absence of rectal emptying (*Tables 2* and *3*).

There was no consistent pattern of success or failure associated with previous vaginal delivery, anal surgery or hysterectomy. However, there was a discrete group of ten patients who did not improve, all of whom had abnormal anorectal physiology and who had previous vaginal delivery (*Fig. 1*). Seven patients who did improve had previous vaginal delivery but these patients all had normal anorectal physiology.

Follow-up

On follow-up for at least 1 year after treatment, all nine patients who had successful biofeedback treatment remained well. One of the two patients who abandoned biofeedback has continued with conservative management; the other had a colectomy and ileorectal anastomosis. With regard to the 19 patients who did not improve after biofeedback treatment, six patients had a stoma constructed, three patients refused the offer of a stoma, two patients defaulted from follow-up, one patient had a colectomy and ileorectal anastomosis, six continued with conservative management and one moved out of the area (*Fig. 2*). All six patients who had a stoma achieved symptom relief and one patient who had colectomy and ileorectal anastomosis after failed biofeedback also improved.

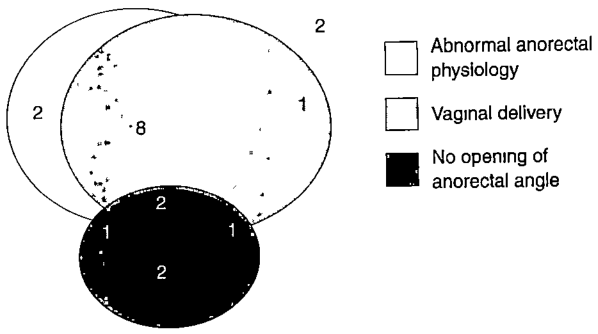

Fig. 1 Anorectal physiology and history of vaginal delivery in 19 patients who did not improve after biofeedback The largest group who did not improve comprised the ten patients who had previous vaginal delivery associated with abnormal pelvic floor physiology

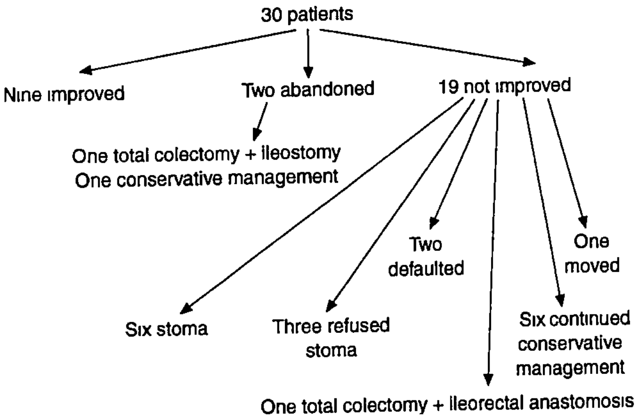
30 patients
Nine improved
Two abandoned
19 not improved
One total colectomy + ileostomy
One conservative management
Two defaulted
One moved
Six stoma
Three refused stoma
Six continued conservative management
One total colectomy + ileorectal anastomosis

Fig. 2 Outcome in 30 patients with outlet obstruction constipation who had biofeedback. One patient who has not improved is considering stoma formation

Discussion

This study has demonstrated that biofeedback is not successful in all patients with outlet obstruction constipation. This is probably because the patient group is not homogeneous. Different case selection, different regimens and different methods of biofeedback may explain the variability in success rate between previous studies.

In the present study failure to evacuate at evacuating proctography, inability to expel a balloon and increased sphincter pressure during attempts to evacuate were used to select patients from those with severe symptoms of constipation who had failed to improve with medical management. Any investigation of defaecation must be performed in artificial circumstances. Dynamic integrated proctography was not performed[16]. Although there would be additional information from integration of investigations, the authors believe there is some benefit in performing several different investigations of defaecation in different circumstances. Intrarectal pressure was not measured and it may be that some patients were included who 'did not strain enough'. Although these patients might not fit Roberts and colleagues' description of outlet obstruction constipation[16], they might well be helped by biofeedback.

Biofeedback was not helpful in patients who had deranged pelvic floor physiology. These patients probably sustained neurological damage to the pelvic floor during childbirth. Snooks *et al.*[17] have described the separate innervation of the puborectalis and external sphincter and have suggested that in some constipated patients damage to more than one innervation may occur rather than pudendal neuropathy alone. It may be that differential damage to the nerves and muscles of the pelvic floor can occur, leading to problems with defaecation due to disordered pelvic floor contraction in some individuals. If this damage is severe, it may not be possible to improve the situation with biofeedback training. It is also logical that biofeedback was unsuccessful in patients with severely blunted rectal sensation since functioning sensory afferents are presumably required to detect rectal fullness and the need for defaecation. This would be consistent with previous damage to these nerves.

It is disappointing that patients with failure to open the anorectal angle and no other abnormality of pelvic floor physiology were not helped by biofeedback. Others have had greater success. In one report[18] 36 of 40 patients with puborectalis paradox were symptomatically improved even though 31 still had demonstrable puborectalis paradox after treatment; it may be significant that 24 of the 62 patients studied were male. The great majority of patients seen in the UK with severe functional constipation are female and perhaps the group studied in Singapore had different aetiologies. Puborectalis paradox is a particularly ill understood abnormality. Indeed this radiological finding has been seen in up to 50 per cent of normal individuals[19]. Unfortunately the present study has only emphasized failure in this difficult area. Botulinum toxin A has been used in the treatment of dystonia elsewhere in the body. Two reports of its use in puborectalis paradox have been encouraging[20,21].

In this study the demonstration of retained colonic markers in addition to a pelvic floor problem did not reduce the chance of success with biofeedback. It may be that outlet obstruction constipation is the primary problem causing prolonged colonic transit in some individuals. Successful treatment of the emptying problem would then lead to resolution of the delay in transit. In patients who appear to have both prolonged colonic transit and outlet obstruction constipation it seems logical to use biofeedback to treat the pelvic floor problem before considering major surgery for slow transit. At least biofeedback is free of complications.

Many others have pointed out the high incidence of anxiety and psychological problems in patients with severe constipation. According to the present data a positive psychological history does not preclude success in biofeedback therapy, perhaps because the support of the biofeedback nurse helps the psychological difficulties as well as the pelvic floor problem. Leroi and colleagues[22] have already shown that the combination of psychotherapy and biofeedback is a useful approach. The Cleveland Clinic group have recently reported their results with biofeedback[23]. The description of their methodology emphasizes many aspects of treatment other than the biofeedback therapy itself. Seventy per cent of their patients discharged themselves from biofeedback therapy before the therapist was happy about the outcome, and outcome was significantly associated with willingness and ability to attend at least five sessions of treatment. It may be that those who benefit most from biofeedback have psychological difficulties as the dominant cause of their problem.

The mechanism underlying biofeedback is unknown. It may be that the input of an interested nurse specialist is as important as biofeedback itself. Muscle training alone may be as effective as biofeedback[24] although others have failed to show any improvement in symptoms after non-specific relaxation treatment such as yoga[25].

In conclusion, the present study confirms that biofeedback is useful in some patients with severe constipation, particularly those with outlet obstruction constipation who have relatively normal pelvic floor physiological tests. Patients who appear to have slow transit and outlet obstruction should be treated with biofeedback in the first instance. Biofeedback is more likely to be successful in patients who do not have evidence of severe pelvic floor damage.

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Original article

Prospective comparison of endosonography, magnetic resonance imaging and surgical findings in anorectal fistula and abscess complicating Crohn's disease

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Background: Endosonography and magnetic resonance imaging (MRI) are promising methods for evaluating perineal and anorectal fistulas or abscesses. The aim of this study was to compare the results of anal endosonography (AES), MRI and surgical exploration in the assessment of anorectal fistula or abscess complicating Crohn's disease.
Methods: Twenty-two patients with Crohn's disease, seven men and 15 women of mean age 38 (range 17–67) years, were included in this prospective study. All patients underwent AES (linear probe 7 MHz), MRI and operative assessment.
Results: AES and MRI demonstrated 14 and nine abscesses respectively, whereas 11 abscesses were confirmed by surgical exploration in ten patients. The sensitivity of AES and MRI as means of evaluating anorectal abscesses was 100 and 55 per cent respectively. The agreement per patient was 86 per cent (19 of 22) for AES and 59 per cent (14 of 22) for MRI. AES and MRI demonstrated 26 and 14 fistulas respectively, whereas 27 fistulas were confirmed during surgical exploration in 16 patients. The sensitivity of AES and MRI was 89 and 48 per cent respectively. The level of agreement per patient was 82 per cent (18 of 22) for AES and 50 per cent (11 of 22) for MRI.
Conclusion: AES with a linear probe is more accurate than MRI in detecting anorectal abscesses complicating Crohn's disease, and much more accurate in the evaluation of complex fistulas.

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Introduction

Perianal sepsis occurs in 4–52 per cent of patients with Crohn's disease. The incidence of perianal disease depends on the region of the intestine involved with Crohn's disease[1–3]. Anal involvement has been documented in about half the patients with colonic disease[2], and in nearly 100 per cent with rectal disease[3]. The silent growth of these lesions leads to late diagnosis of abscesses or fistulas[4]. Moreover, perianal manifestations of Crohn's disease are likely to be followed by postoperative recurrence and incontinence. Medical or surgical management is difficult because the fistulas are often extensive and complex. Clear images of perianal Crohn's lesions are therefore required to limit the risk of operative trauma to the anal sphincters.

Fistulography and computed tomography (CT) have been disappointing[5,6]. Anal endosonography (AES) and magnetic resonance imaging (MRI) have recently been evaluated for anorectal abscesses and fistulas[7–14]. The accuracy of AES and MRI has been variably estimated, ranging from 63 to 100 per cent and from 84 to 91 per cent respectively[6–14]. Only one prospective study[12] on 20 patients has compared the results of MRI and AES with operative findings; only five patients had Crohn's disease. The accuracy of AES may have been underestimated, since rotating endoprobes providing radial scan images are commonly used. With this technique, fistula *in ano* shows up in the form of a white dot surrounded by a hypoechoic area corresponding to an air bubble in an inflammatory fistula track. With linear probes, a fistula may be traced along its whole route, from the internal opening. The image is represented as a continuous column of echo-rich bubbles[15].

The aim of this study was to compare MRI and AES using a linear probe in a prospective single-blind assessment of complex perianal lesions.

Patients and methods

Twenty-three patients with clinical symptoms of perianal Crohn's disease were enrolled in this prospective study between 1996 and 1998. One patient was excluded because of a stenosis which ruled out anal endosonography. All had radiologically or endoscopically proven Crohn's disease with clear histological criteria. There were seven men and 15 women with a mean age of 38 (17–67) years. The mean duration of the Crohn's disease was 8 (1–20) years. In three patients perianal complications were the presenting manifestation. In 14 other patients, the onset of the disease had occurred fewer than 5 years previously. Eight patients had previously had surgery for ileocolonic stenosis (three patients) or anorectal fistulas or abscesses (five). At the time of the study, ten patients were taking corticosteroids, eight immunosuppressive drugs (azathioprine or methotrexate) and four a combination of ciprofloxacin and metronidazole. Only three patients were not receiving medical treatment. All patients had AES, MRI and examination under anaesthesia followed by surgical treatment as necessary. All investigations were carried out without knowledge of previous findings.

Anal endosonography was performed 1–2 days before surgery by the same examiner. A rigid linear endoanal probe with a frequency of 7 MHz was used (model PVL-625RT; Toshiba, Tokyo, Japan). The probe was 20 mm wide and 120 mm long with a field of view of 57 mm. Patients were examined in the left lateral decubitus position. The tip of the probe was covered by a water-filled balloon to maintain acoustic coupling. By rotating the linear probe through 360°, the anal wall layers (mucosa, internal sphincter, external sphincter) and the perirectal tissues (urinary bladder, vagina or prostate) could be identified.

MRI was performed on a high-field machine operating at 1 T (Magnetom SP 1·0 Tesla; Siemens, Erlangen, Germany), after AES but before surgery. All patients had T_1- and T_2-weighted spin echo acquisitions performed in the axial plane. Subsequent to an intravenous injection of gadolinium (0·2 ml/kg), T_1-weighted spin echo sequences were acquired in the coronal, axial and sagittal planes. All examinations were performed with a body coil. Images obtained were analysed by the same investigator, without previous knowledge of the results of AES.

Operative assessment was done with patients placed in the lithotomy position. Examinations were performed under general anaesthesia with careful visual control, using an anal retractor and special probes for cannulating the fistula track. The sites of any external and internal openings, the number and direction of fistula tracks, and the sites of fluid collections were recorded. Surgical findings were considered as the 'gold standard' for data analysis.

All assessments were recorded under blind conditions on separate sheets. Sensitivity, specificity, positive predictive value and negative predictive value were calculated. Agreements per patient were taken to be the proportion of concordant results between AES or MRI and operative assessment.

Results

Perianal abscess

At operation, 11 abscesses were identified in ten patients. Two were horseshoe fluid collections; the location of the remaining abscesses was anterior in five patients, posterior in two and lateral in two. AES located 14 abscesses measuring 8–37 mm. No false negatives occurred but three false positives were found in comparison with the operative assessment. In two cases, the presence of a large hypoechoic area around an internal opening was misinterpreted as an intersphincteric abscess. At operation, no pus was observed at the level of the internal opening. In the remaining patient, thrombosis of the external haemorroidal plexus was misdiagnosed as a superficial abscess. At MRI, nine abscesses were detected (*Fig. 1*); five

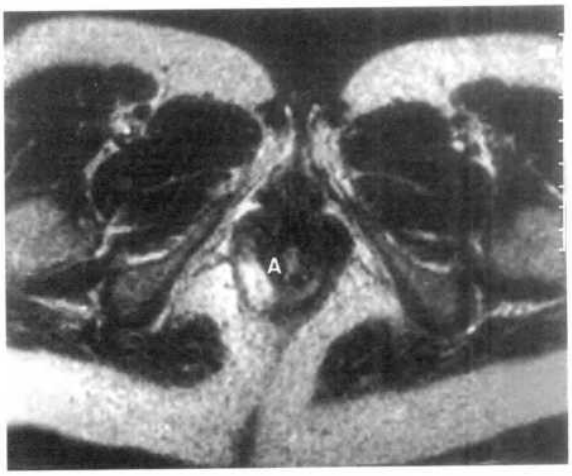

Fig. 1 Axial T_2-weighted magnetic resonance image of a trans-sphincteric abscess (A) contrasting with the remaining anal canal

false-negative and three false-positive examinations were recorded. The five false-negative MRIs were taken in three patients to be inflammatory areas 6, 11 and 28 mm in size, a residual cavity of 10 mm in one and an abscess (30 mm in size) missed in one patient who had two abscesses and a complex fistula. The three false-positive MRIs were recorded in patients who had a fistula *in ano*, but no abscess. In one, an abscess measuring 2 cm was also detected at AES. The sensitivity, specificity, positive predictive value and negative predictive value of AES and MRI are shown in *Table 1*. Among the 22 patients assessed by operative exploration, the level of agreement per patient was 19 with AES (86 per cent) and 14 with MRI (59 per cent).

Fistula *in ano*

Twenty-seven fistulas were diagnosed in 16 patients at operation. Eleven patients had multiple or complex fistulas; five had a single fistula *in ano*. Sixteen internal openings were detected at surgery: anterior in eight, posterior in three and lateral in five. Fourteen internal openings were detected by AES and three by MRI. The 27 fistulas were classified as follows at surgery: four intersphincteric, nine trans-sphincteric, one suprasphincteric, five extrasphincteric, one supralevator, two infralevator and five anovaginal. In one patient, an anovaginal fistula was observed at AES but could not be detected at operation. Some 15 days later, the patient returned to hospital with pus in the vagina. A further operative exploration uncovered the anovaginal fistula demonstrated at AES (*Fig. 2*).

Twenty-six fistulas were recorded at AES. There were three false-negative results in patients with multiple fistulas detected at the operative assessment. There were two false-positive AES examinations in two patients. In one a fistula was thought to exist with a lateral direction at AES. At MRI a large posterior abscess involving the whole length of both anal sphincters was seen. Although the abscess was detected at surgery, the fistula was not identified. In the remaining false-positive case, the patient was thought to have multiple fistulas at AES, but this was not confirmed at the operative assessment. Fourteen fistulas were diagnosed using MRI, including 14 false negatives and one false positive. The false positive involved the patient previously reported, who had a large posterior abscess and a fistula detected at AES. Sensitivity, specificity, positive predictive value and negative predictive value in AES and MRI are shown in *Table 2*. Among the 22

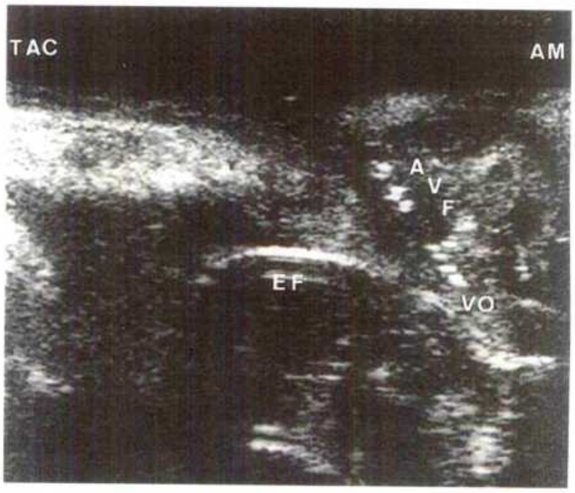

Fig. 2 Anal endosonographic image of an anovaginal fistula (AVF) which shows up a continuous column of echo-rich bubbles. The examiner's finger (EF) is inside the vaginal lumen close to the vaginal opening (VO) of the fistula. The orientation is given at the top of the image: AM, anal margin; TAC, top of anal canal

Table 1 Results of anal endosonography and magnetic resonance imaging in the diagnosis of perianal abscess

	AES	MRI
Total no. of abscesses diagnosed*	14	9
True positive	11	6
False negative	0	5
False positive	3	3
Agreement per patient	19 of 22 (86)	14 of 22 (59)
Sensitivity (%)	100	55
Specificity (%)	77	77
Positive predictive value (%)	79	67
Negative predictive value (%)	100	67

Values in parentheses are percentages. *Eleven abscesses were found at operation. AES, anal endosonography; MRI, magnetic resonance imaging

Table 2 Results of anal endosonography and magnetic resonance imaging in the diagnosis of fistula *in ano*

	AES	MRI
No. of fistulas diagnosed*	26	14
True positives	24	13
False negatives	3	14
False positives	2	1
Agreement per patient	18 of 22 (82)	11 of 22 (50)
Sensitivity (%)	89	48
Specificity (%)	66	80
Positive predictive value (%)	92	93
Negative predictive value (%)	57	22

Values in parentheses are percentages. *Twenty-seven fistulas were found at operation. AES, anal endosonography; MRI, magnetic resonance imaging patients assessed at operation, the level of agreement per patient was 18 with AES and 11 with MRI.

Discussion

It has been suggested that local surgery for anoperianal Crohn's lesions should be limited because of the risk of faecal incontinence[3,4]. In a recent series of 66 patients with Crohn's disease treated by local surgery 40 (61 per cent) continued to have a functional anus[2]. Since many fistulas are not explored surgically, little is known about the natural history of suppurative lesions complicating Crohn's disease[16]. Whether or not a patient has surgery, there is a need for accurate imaging of perianal Crohn's lesions. Fistulography yielded little information about the anatomical relationships[3]. CT provided poor-quality imaging of the anorectal wall and was less reliable than AES[6,17]. Two recently developed techniques, MRI and AES, could yield a better delineation of fistulas and perianal abscesses. Only one prospective study comparing these two techniques with surgical assessment has been published to date[12].

The results of MRI in the present series seem less accurate than those in previous reports. Here, a sensitivity of 55 per cent and a positive predictive value of 67 per cent were obtained for the diagnosis of abscess, with a sensitivity of 48 per cent and a positive predictive value of 93 per cent for the diagnosis of fistula. However, all the patients in this series had Crohn's disease, and 11 of 16 had multiple and complex fistulas. This may account for the low accuracy of MRI. In a previous prospective study, Lunniss *et al.*[12] investigated 35 patients, although only five had Crohn's disease. The MRI findings in 20 of the patients were compared with those obtained with AES. The accuracy of MRI was 86 per cent for the diagnosis of fistula, 91 per cent for the diagnosis of abscess and 80 per cent in detecting internal openings. MRI was thought to be more accurate than AES for abscesses of the ischiorectal fossa and supralevator area. Haggett *et al.*[13] compared MRI and clinical findings, but in seven patients the clinical assessment was performed before MRI and in 18 afterwards. Abscesses or fistulas were detected in 16 patients, and were multiple in ten. MRI showed the existence of additional fistulas or abscesses in three patients, with one false negative. A recent series of 18 patients, four of whom had Crohn's disease, was reported by Tissot *et al.*[14]. Internal openings were detected by MRI in 11 of the 15 patients assessed surgically. Fistulas were detected in the 16 patients at operation, but there was one false-positive finding[14]. The ten abscesses in this series were correctly diagnosed[14]. In the present study, body coils and not phase-array coils or endoanal coils were used. With an endoanal coil, the depiction of the normal anal sphincter on MRI might be improved[18].

Numerous studies of patients with and without Crohn's disease have been carried out to determine the accuracy of AES for diagnosing abscess and fistula *in ano*[6–12,15]. All but one were performed with a rotating endoprobe[15]. The overall concordance between MRI and surgery was higher than between AES and surgery[12]. The respective rates were 85 and 65 per cent, but the difference was not statistically significant[12]. In previously published series, the accuracy of AES for the diagnosis of abscesses ranged from 63 to 100 per cent[6–9,11]. In two of these studies using radial probes, AES was incapable of identifying suprasphincteric or extrasphincteric primary tracks and secondary supralevator and infralevator tracks[8,11]. In the present study, AES was accurate in the diagnosis of abscesses in 86 per cent (19 of 22). The focal depth of the probe in this study was 57 mm, which made it possible to examine part of the ischiorectal fossa and the supralevator area. A fistula can probably be assessed more accurately with a linear probe because it shows up as a continuous column of echo-rich bubbles. In previous series, the accuracy of AES for the diagnosis of fistulas ranged from 48 to 94 per cent[6,8,10,11]. Despite the presence of multiple or complex fistulas in 11 of 16 patients in the present study, the accuracy of AES was 82 per cent (18 of 22). In addition, one anovaginal fistula was detected at AES that was not identified by the surgeon at first examination. The ability of the linear probe to follow the echo-rich bubbles moving along the fistula track obviated the need for enhancing injections of hydrogen peroxide[19]. In previous studies, internal openings were detected with AES in 11–75 per cent, compared with 14 of 16 patients in the present investigation[8,10,11].

Anal endosonography, particularly when performed with a linear probe, provides clear anatomical details of anal abscesses and an excellent picture of fistula tracks. The relationship between anal sphincters and the primary or secondary tracks of an anal fistula can be assessed accurately.

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Three-dimensional endoanal sonography in assessing anal canal injury

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Background: Instrument design limits endosonography of the anal canal to the axial plane, with no capability for longitudinal imaging or measurement. Using three-dimensional reconstructions, the relationship between the radial and linear extent of an anal sphincter tear has been explored, and sex differences in anal canal and sphincter length have been established.

Methods: Three-dimensional reconstructions were performed in 20 controls and 24 patients with faecal incontinence found to have 25 external and five internal sphincter defects. The radial and linear extent of any sphincter tear was measured. In controls the length of the sphincters was compared with the total anal canal length, and the maximum and mean internal sphincter thickness was compared.

Results: The radial angle of an internal or external sphincter defect was significantly related to its length ($R^2 = 96{\cdot}8$ per cent and $R^2 = 84{\cdot}4$ per cent respectively; both $P < 0{\cdot}001$). The anal canal was longer in men than in women (mean(s.d.) 32·6(5·3) *versus* 25·1(3·4) mm; $P < 0{\cdot}001$). The internal anal sphincter was also longer in men (25·6(6·3) *versus* 19·8(4·0) mm; $P < 0{\cdot}02$), but the mean internal sphincter length as a percentage of total anal canal length did not differ (78·3 *versus* 78·7 per cent; *P* not significant). The anterior external anal sphincter was longer in men than in women (32·6(5·3) *versus* 15·3(2·8) mm; $P < 0{\cdot}001$), and formed a greater percentage of total anal canal length (100 *versus* 62·9 per cent; $P < 0{\cdot}001$).

Conclusion: Multiplanar imaging has revealed a direct relationship between the length of a sphincter tear and its radial extent as shown on axial scanning. Marked sex differences in sphincter configuration have been demonstrated. In women the shorter anterior sphincter length highlights the risk of complete sphincter disruption with extensive tears.

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Introduction

Anal incontinence for gas or faeces affects up to 11 per cent of adults and occurs frequently in 2 per cent. The commonest cause in otherwise healthy women is sphincter damage incurred during vaginal delivery[1].

Much of the understanding of the importance of sphincter damage has resulted from detailed imaging of the sphincter complex obtained by endoanal sonography[2]. The ultrasound system developed specifically for this examination employs a mechanically rotated single crystal. Inherent in this design is that it produces only a thin cross-sectional image of the anal canal (*Fig. 1*). Various levels of the canal may be recognized[3], and the longitudinal extent of an abnormality can be described in these imprecise terms only. During scanning it is possible to appreciate the longitudinal extent of both normal structures and any abnormality, although no accurate measurement is possible. Sex differences in external sphincter morphology have been shown[4]. Detailed studies using magnetic resonography with an endocoil and multiplanar imaging have confirmed these sonographic findings[5].

Most studies have concentrated on establishing the accuracy of endosonography in detecting sphincter tears by comparison to either electromyography[6,7], surgery[8], or a combination of surgery and histology[9] where a sensitivity and specificity of 100 per cent was reported. The configuration of any tear throughout the canal has been largely ignored. Yet the main indication for endosonography is to detect patients with faecal incontinence who have a sphincter defect amenable to surgical repair. The benefits of this have been confirmed in several studies[10–13].

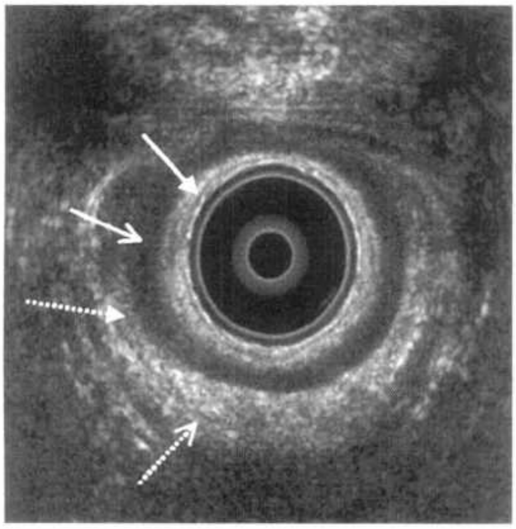

Fig. 1 Conventional two-dimensional endoanal ultrasonographic image in the transverse plane. The subepithelium (solid arrow) can be seen encircling the bright interface reflection from the outer rim of the plastic nose cone. The hypoechoic internal sphincter (solid open arrow) is a low reflective ring. The longitudinal muscle (dotted arrow) is a moderately reflective layer, within the striated texture of the external sphincter (dotted open arrow)

Although absolute continence is not always restored, there is usually worthwhile improvement. Postoperative failure has been related to persisting sphincter defects[10], even though the angular measurement of the defect may have been decreased[14]. It is possible that the anterior ring of external sphincter may be restored at one level, but remain incomplete at another[12]. Conventional axial imaging does not give an accurate picture of the length of a sphincter tear to the operating surgeon, to judge how far the repair should extend.

Three-dimensional endoanal sonography produces a digital volume that may be viewed and measured in any plane. Using this facility, the possible relationship between the radial angle and longitudinal extent of a sphincter defect was investigated. Sex differences apparent in sphincter and canal length were also quantified, as these may be relevant to the impact that a tear of given length has on sphincter function.

Patients and methods

Three-dimensional reconstructions of axial endosonography were performed on 24 consecutive patients (mean age 48 (range 31–72) years; 21 women) found to have sphincter defects on endosonography. There were 25 external defects in 20 patients: 24 tears in 19 women from old obstetric trauma and one postsurgical defect in a man. There were five internal sphincter defects (in three women and two men), two after sphincterotomy for fissure and three following fistulotomy for sepsis.

Reconstructions were also performed in 20 subjects with a normal anal canal on endosonography, normal manometry and no previous anal surgery; there were ten women, all parous, of mean age 59 (range 33–83) years and ten men of mean age 38 (range 25–55) years.

Stepped movement of the probe was achieved with a mechanical rig at 1·25-mm intervals, captured on a personal computer video card. The data set was then rendered and analysed.

Any sphincter defect was viewed in the axial plane to display the maximal radial extent of the defect. The angle between the two ends of the defect and the centre of the probe was then measured using the electronic callipers within the program (*Figs 2a* and *3a*).

The longitudinal extent of the external sphincter defect was also determined. The proximal (*Fig. 2a*) and distal (*Fig. 2b*) limits were found and the slice levels recorded. This subvolume was isolated and its length measured. Measurement of an internal sphincter defect length was easier, as this could be discerned from a coronal or sagittal cut in the plane of the defect (*Fig. 3b*).

The angle of the defect was then related to its longitudinal extent. Internal and external anal sphincter defects were compared in combination and separately.

Control group measurements

Anal canal length

The anal canal length was the distance measured between the proximal canal (considered to begin where the puborectalis muscle became clearly defined) and the lower border of the subcutaneous external sphincter.

Internal sphincter length

The mean length was calculated from the measurements of both sides of the internal sphincter in the mid-coronal plane.

Internal sphincter thickness

The internal sphincter thickness was measured in two ways. The maximum thickness was measured in the 3 or 9 o'clock position at any point along the length of the sphincter. The mean thickness was then determined from

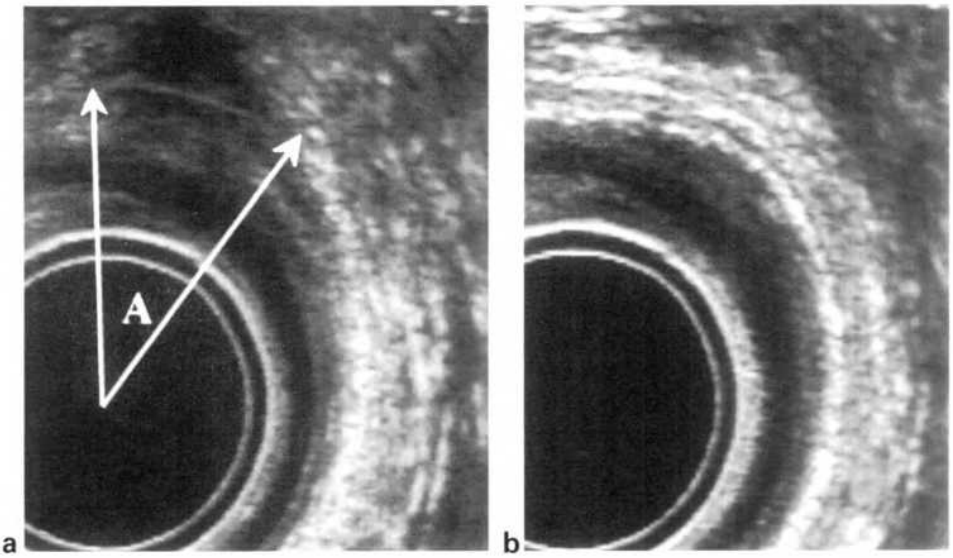

Fig. 2 **a** The maximal angular extent of the external sphincter defect (between arrows) is measured in the axial plane as an angle (A). **b** The external sphincter is now intact defining the lower border of the tear

measurements at 3, 6, 9 and 12 o'clock at the anatomical midpoint of the sphincter.

Anterior external sphincter length

The anterior aspect of the external sphincter was measured in the mid-sagittal plane, from the proximal formation of a complete ring to the termination of the subcutaneous external sphincter distally.

Statistical analysis

All sets of data underwent an F test for normal distribution. Parametric data were analysed using paired or unpaired t tests, and non-parametric data using the Mann–Whitney test. Microsoft Excel V7 (Microsoft, Seattle, Washington, USA) and GraphPad Prism V2 (GraphPad Software, San Diego, California, USA) were used for analyses and production of graphs.

Results

A successful three-dimensional reconstruction was achieved from every examination.

The 25 external sphincter defects had a mean defect angle of 55° (range 26–140°) and a mean length of 7 (range 2–19) mm. Regression analysis gave a coefficient of determination (i.e. the degree to which the change in defect length can be explained by a change in radial angle) as $R^2 = 84{\cdot}4$ per cent ($P < 0{\cdot}001$). The five internal

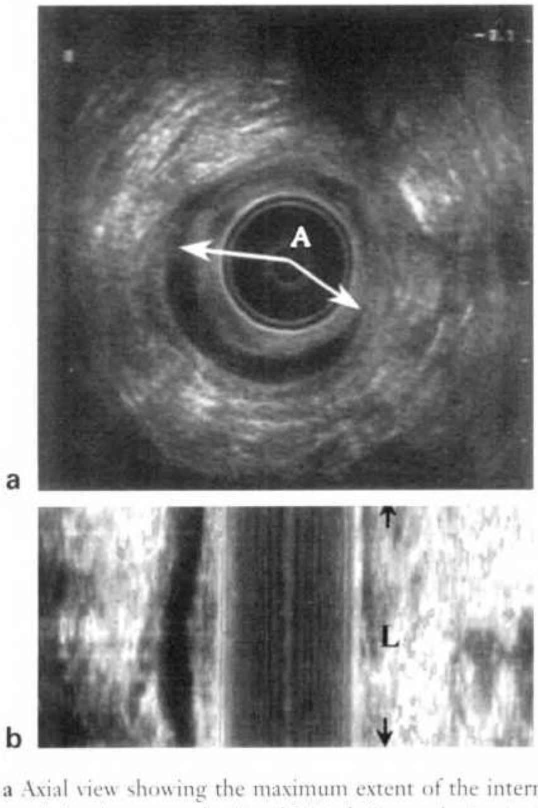

Fig. 3 **a** Axial view showing the maximum extent of the internal sphincter defect has an angle (A) of 201°. **b** Coronal view in the plane of the defect, showing that this extends the full length of the internal sphincter, with a length of 29 mm. L, left

sphincter defects had a mean defect angle of 115° (range 62–201°) and a mean length of 19 (range 11–29) mm. Regression analysis gave $R^2 = 96{\cdot}8$ per cent ($P < 0{\cdot}001$). Regression analysis of all defects gave $R^2 = 83{\cdot}7$ per cent ($P < 0{\cdot}001$) (*Fig. 4*).

In the control group, the mean(s.d.) male anal canal length was 32·6(5·3) mm, significantly longer than the female length (25·1(3·4 mm)) ($P < 0{\cdot}001$; 95 per cent confidence interval (c.i.) 3·4–11·8 mm).

The mean(s.d.) internal sphincter length for men was 25·6(6·3) mm, while the female internal sphincter was significantly shorter at 19·8(4·2) mm ($P < 0{\cdot}02$; 95 per cent c.i. 0·9–10·9 mm). The mean(s.d.) male internal anal sphincter length as a proportion of the total canal length was 78·3(8·2) per cent, similar to that for women (78·7(9·0) per cent) ($P < 0{\cdot}91$; 95 per cent c.i. −7·7 to 8·5 mm). The mean(s.d.) male maximal internal sphincter thickness was 1·9(0·5) mm and the male 'mean internal sphincter thickness' was 1·5(0·4) mm. These two values were significantly different ($P < 0{\cdot}001$, paired t test; 95 per cent c.i. 0·2–0·7 mm). The mean(s.d.) female maximal internal sphincter thickness was 2·6(0·7) mm and the female 'mean internal sphincter thickness' was 1·9(0·6) mm ($P < 0{\cdot}001$; 95 per cent c.i. 0·4–1·0 mm). The difference between male maximal thickness (1·9 mm(0·5 mm)) and female maximal thickness (2·6(0·7 mm)) was significant ($P = 0{\cdot}02$, unpaired t test; 95 per cent c.i. 0·1–1·2 mm). The difference between male mean thickness (1·5(0·4 mm)) and female mean thickness (1·9(0·6) mm) was also significant ($P < 0{\cdot}05$; 95 per cent c.i. 0·0–0·9 mm).

The mean(s.d.) anterior external sphincter length was 32·6(5·3) mm in men and 15·3(2·8) mm in women ($P < 0{\cdot}001$; 95 per cent c.i. 13·4–21·4 mm). The median (interquartile range percentage ratio of external sphincter to canal length in men was 100 (0) per cent compared with 62·9 (53·8–70·7) per cent in women ($P < 0{\cdot}0001$).

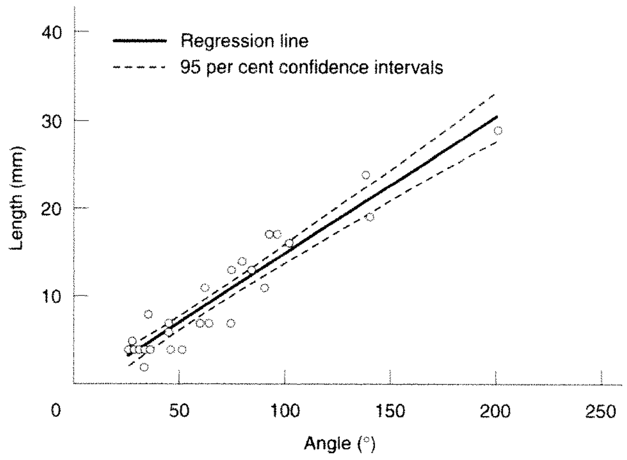

Fig. 4 External and internal anal defect angles plotted against length. $R^2 = 83{\cdot}7$ per cent; $P < 0{\cdot}001$

Discussion

Although the external and internal sphincters are very different in morphology, both represent an arrangement of muscle fibres with an inherent resting tone held in place by the fibroelastic mesh of the longitudinal muscle[15]. The part of the sphincter that is disrupted will be subjected to tension from the resting tone of the remaining sphincter and the fibroelastic mesh. It is therefore perhaps not surprising that there should be a linear relationship between the length of a tear, and how far its ends have pulled apart. This relationship is comparable for both sphincters, suggesting that the tension of the fibroelastic mesh may be of more importance than the inherent tone of the sphincter, which is significantly different.

The main reason for performing endoanal ultrasonography in incontinent patients is to distinguish idiopathic incontinence from sphincter defects and to provide accurate anatomical information about the sphincter anatomy and configuration before surgical repair[11]. The benefit of sphincter repair has been demonstrated, with functional improvement in 76–93 per cent of cases and a postoperative increase in maximum squeeze pressure of up to 11–15 $\mathrm{cmH_2O}$[10,12,13]. Outcome is further improved if postoperative sonographic assessment confirms an intact external anal sphincter ring. One study showed an improvement in 32 of 35 patients in whom the external anal sphincter was intact compared with five of 11 in whom a defect persisted[10]. A wide transverse tear, of either the internal or external sphincter, reported on endosonography should alert the surgeon that the tear will be of proportionate length. This might help eliminate incomplete repairs due to inadequate dissection, should the full extent of the defect not be appreciated from preoperative imaging.

Sex differences in anal canal morphology have been suggested using magnetic resonance imaging (MRI)[5,16], endoanal ultrasonography[4] and transvaginal ultrasonography[17], but no published study gives detailed comparisons of longitudinal measurements. In this study the internal sphincter thickness was similar to that reported previously, although the statistical difference between men and women is unlikely to be of clinical significance.

The maximal and mean thickness of the internal sphincter differed, indicating that the sphincter is not of uniform thickness in either sex. This explains discrepancies in comparative studies of sonographic measurements[18]. However, assessment of the internal sphincter

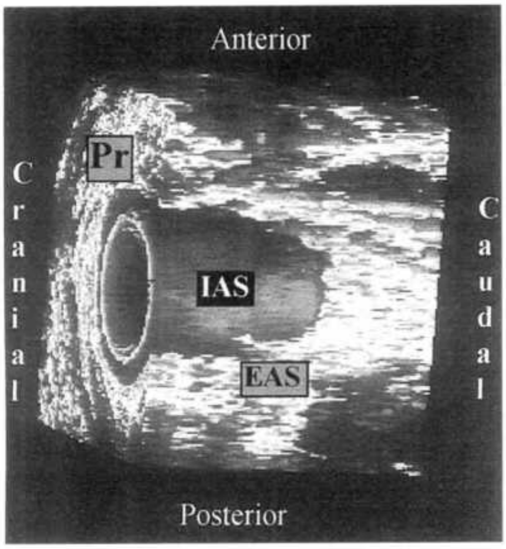

Fig. 5 Three-dimensional representation of the male anal canal viewed in the right oblique plane, sliced through the right side of the internal sphincter. The puborectalis (Pr) at the proximal aspect of the canal is difficult to distinguish from the external anal sphincter (EAS). In contrast to that in women, the male EAS is present along the full length of the canal anteriorly. The internal anal sphincter (IAS) terminates approximately in the mid-canal level. The subcutaneous external sphincter is longer in this patient than in the female example

thickness is important, as an abnormally thin sphincter has significance in passive incontinence[19], and an abnormally thick sphincter for the patient's age suggests solitary rectal ulcer syndrome[20].

The absolute internal sphincter lengths are also different between the sexes but this would appear to be a function of the anal canal length, as the percentage ratios of the internal sphincter lengths were not different. As suggested previously[21] this is relevant in women undergoing sphincterotomy, as an incision of a given length will divide proportionally more of the sphincter in women than in men.

A further sex difference in anal sphincter morphology lies in the arrangement of the anterior part of the external sphincter. In men the anterior part is present along the entire length of the canal (*Fig. 5*). In women, not only is it shorter but its length as a percentage ratio of the entire canal length varies widely (*Fig. 6*). This shorter anterior ring of the external sphincter has been described sonographically[4] and on MRI[22,23], although not measured in detail. Presumably stretching of the shortened anterior component confers some protection during childbirth. However, when it does tear, most of the anterior sphincter will be involved.

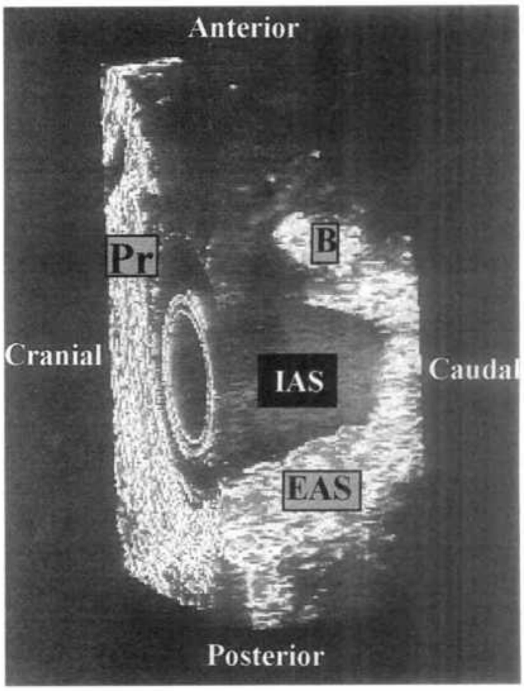

Fig. 6 Three-dimensional representation of the female anal canal viewed in the right oblique plane, sliced through the right side of the internal sphincter. The left side of the U-shaped puborectalis (Pr) can be seen at the proximal end of the canal. The right aspect of the internal anal sphincter (IAS) terminates approximately two-thirds of the way down the canal. The external anal sphincter (EAS) is seen to form an anterior ring just before the termination of the IAS and continues as the subcutaneous external sphincter. The bulbospongiosus muscle (B) is anterior to the EAS

Since its introduction, endosonography has described the longitudinal anatomical differences between the sexes, and the extent of traumatic damage to the sphincters. Volume reconstruction of axial images to produce multiplanar sectioning of the anal canal has allowed these components to be quantified. This has clarified the normal anatomy and highlighted a direct relationship between the radial and longitudinal extent of sphincter tears which may be of value in surgical management.

Acknowledgements

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Intraobserver and interobserver agreement in anal endosonography

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Background: The aim of this study was to determine intraobserver and interobserver agreement for sonographic measurements of anal canal structures using anal endosonography (AES), and to determine interobserver agreement for the diagnosis of anal sphincter disruption.
Methods: Fifty-one consecutive patients referred for AES for the investigation of possible sphincter abnormality were examined. Studies were reviewed by two observers who measured anal canal structures at defined levels and locations, and recorded an opinion on sphincter integrity. Repeated measurements made by each observer were compared to determine intraobserver agreement, and measurements and diagnoses were compared between observers to determine interobserver agreement.
Results: Intraobserver agreement was better than interobserver agreement for measurements of anal canal structures. Interobserver limits of agreement for external sphincter measurements spanned 5 mm, whereas those for the internal sphincter spanned 1·5 mm. Interobserver agreement for diagnosis of sphincter disruption and internal sphincter echogenicity was very good ($\kappa = 0{\cdot}80$ and 0·74 respectively).
Conclusion: The limits of agreement for intraobserver and interobserver measurements of anal canal structures on AES have been defined. Interobserver assessment of sphincter disruption is very good.

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Introduction

Imaging the anal sphincters with anal endosonography (AES) has altered opinions about the pathogenesis, investigation and management of anal sphincter disorders[1]. Since its development[2], AES has been used to characterize sphincter abnormalities in anal incontinence[3,4], constipation[5,6], fistula disease[7] and anal pain[8], and to image the sphincters after operation[9]. Findings can be broadly divided into two groups: loss of sphincter integrity and generalized changes in sphincter morphology. While loss of sphincter integrity has been positively correlated with physiological abnormality[3], there has been less success when attempting to correlate measurements of individual sphincter components with physiological performance in patients with intact sphincters[5,10–15]. Individual anal sphincter components are relatively small, being measured in millimetres, and interface reflections at tissue boundaries makes their delineation less precise. Furthermore, the sphincters may not be symmetrical along their longitudinal axis, resulting in differing thickness at different levels. These factors raise the possibility that measurement may be inaccurate.

The aim of this study was to determine intraobserver and interobserver agreement for sonographic measurements of anal canal structures taken from the same examination and to determine interobserver agreement for the diagnosis of anal sphincter disruption and internal sphincter morphology.

Patients and methods

Fifty-one consecutive adult patients (43 women) routinely referred for AES for the investigation of possible sphincter abnormality were examined. Endosonography was performed using a 3535 ultrasound scanner (B&K Medical, Gentofte, Denmark) with an 1850 axial endoscopic probe and type 6004 10-MHz transducer. A plastic cone 17 mm in external diameter, filled with degassed water, covered the transducer head to allow withdrawal into the anal canal. This transducer has a focal range of 5–45 mm, an axial resolution of less than 0·05 mm and a lateral resolution of 0·5–1·0 mm within the focal range. The probe was covered by a lubricated condom and attached to a mechanical rig fitted with a precision linear translation probe-holder to allow withdrawal through the anal canal at increments of 1·25 mm.

The probe was inserted into the anal canal with the patient in the left lateral position. The base of the rig was placed under the patient's legs to stabilize it and the probe-holder adjusted to secure the probe in alignment along the anal canal axis. The probe was positioned at the level of the upper aspect of the puborectalis, and rotated so that the rectovaginal septum in the female, or prostate in the male, was uppermost on the screen and in a normal orientation for cross-sectional imaging. A personal computer-based acquisition system and high-performance video capture card (CV30; 4C's, Maidenhead, UK) was used to capture the series of sonographic images taken from the video output of the scanner. The frozen image was acquired, the probe withdrawn one increment, and the new position scanned and acquired. This process was repeated until the lower limit of the anal canal was reached; each examination was saved on floppy disk for subsequent review.

Examinations were reviewed by two experienced sonographers (D.M.G. and S.H.) using a personal computer and image analysis software (VoxBlast; VayTek, Fairfield, Iowa, USA), which allowed the captured axial images to be viewed sequentially. Pixel size was set to 0·25 mm so that the images were scaled accurately. Only axial images were viewed and no three-dimensional data were generated. Observers initially reviewed the entire examination and noted any apparent defects of the external anal sphincter (EAS) and internal anal sphincter (IAS). An assessment of IAS echogenicity was also made: normal or increased. Measurements of individual sphincter components were made at four levels: puborectalis, proximal anal canal, mid anal canal and subcutaneous. Puborectalis thickness was measured just proximal to the formation of the EAS. Measurements of EAS, longitudinal muscle and IAS thickness were made in the proximal anal canal, at the most cranial level of the EAS. These measurements were repeated in the mid anal canal, defined as the level at which the EAS formed a complete ring anteriorly. At this level additional measurements of the subepithelial tissues and anterior sphincter ring were also made, the anterior ring being defined as the combined thickness of the EAS and longitudinal muscle at 12 o'clock. Subcutaneous EAS thickness was measured in the distal anal canal, defined as that level immediately below the termination of the IAS. All measurements were taken from the left lateral aspect of the anal canal at 3 o'clock using software callipers accurate to 0·01 mm, excepting measurement of the anterior ring which was made at 12 o'clock. Where sphincter disruption prevented measurement at any level, this was noted on the measurement sheet. The accuracy of the callipers was verified by measuring the outer diameter of the probe cone, which equalled the true measurement of 17 mm.

Each observer was unaware of the other's findings at all times. To assess intraobserver agreement, each observer made two separate assessments of each study, separated by at least 1 week and blinded to previous measurements. Assessment of agreement for categorical data was made using the weighted κ statistic[16]. Assessment of agreement for continuous data was made using the Bland and Altman test statistic[17]. Calculations were performed using Arcus Quickstat 1.0 (Research Solutions, Cambridge, UK).

Results

Categorical data

Both observers agreed in 27 patients with intact sphincters, in eight with isolated EAS defects, in two with isolated IAS defects and in five with combined EAS and IAS defects (*Table 1*). There was disagreement in nine patients regarding the presence or absence of isolated EAS defects, giving a weighted κ statistic of 0·80, indicating 'very good' agreement[18]. Both observers considered the IAS to be of normal echogenicity in 43 subjects and increased in five (*Table 2*). There was disagreement in three subjects, giving a κ statistic of 0·74, indicating 'good' agreement[18].

Table 1 Agreement between two observers for the presence of external and internal anal sphincter defects

	Observer 1				
Observer 2	Intact	EAS defect	IAS defect	Combined defect	Total
Intact	27	1	0	0	28
EAS defect	8	8	0	0	16
IAS defect	0	0	2	0	2
Combined defect	0	0	0	5	5
Total	35	9	2	5	51

EAS, external anal sphincter; IAS, internal anal sphincter. Weighted κ = 0·80

Table 2 Agreement between two observers for internal sphincter echogenicity

	Observer 1		
Observer 2	Normal	Increased	Total
Normal	43	2	45
Increased	1	5	6
Total	44	7	51

κ = 0·74

Table 3 Mean differences and limits of agreement for intraobserver and interobserver measurements of anal canal morphology

	Repeatability											
	Observer 1				Observer 2				Interobserver agreement			
Measurement	Mean 1	Mean 2	Mean difference	Limits of agreement	Mean 1	Mean 2	Mean difference	Limits of agreement	Observer 1	Observer 2	Mean difference	Limits of agreement
Puborectalis	5·8	5·9	−0·05	−1·6 to +1·5	3·7	3·8	−0·1	−2·0 to +1·8	5·8	3·7	2·08	−0·7 to +4·9
Proximal anal canal												
EAS	5·0	5·3	−0·34	−2·0 to +1·3	3·3	3·4	−0·05	−1·7 to +1·6	5·2	3·4	1·83	−0·8 to +4·5
Longitudinal muscle	2·3	2·3	0·04	−1·5 to +1·6	2·5	2·6	−0·14	−1·2 to +0·9	2·3	2·5	−0·21	−1·6 to +1·2
IAS	1·9	1·9	0·004	−0·6 to +0·6	1·8	1·7	0·02	−0·6 to +0·7	1·9	1·8	0·14	−0·6 to +0·9
Mid anal canal												
EAS	4·7	5·0	−0·3	−2·0 to +1·4	3·1	3·1	0·04	−1·4 to +1·5	4·8	3·1	1·48	−1·5 to +4·5
Longitudinal muscle	2·0	2·0	−0·02	−0·9 to +0·8	2·4	2·6	−0·1	−1·6 to +1·4	2·0	2·5	−0·4	−1·7 to +0·9
IAS	2·0	1·9	0·04	−0·7 to +0·8	1·8	1·7	0·12	−0·3 to +0·6	2·0	1·7	0·22	−0·4 to +0·9
Subepithelium	1·4	1·4	0·02	−0·6 to +0·7	1·6	1·5	0·04	−0·5 to +0·6	1·4	1·5	−0·18	−0·8 to +0·5
Anterior ring	3·9	4·1	−0·16	−1·5 to +1·2	4·0	3·9	0·11	−1·5 to +1·7	4·0	3·9	0·08	−1·9 to +2·0
Subcutaneous EAS	6·2	6·3	−0·04	−2·1 to +2·0	6·0	6·1	−0·08	−2·6 to +2·5	6·2	6·1	0·18	−2·4 to +2·8

All measurements are in millimetres. EAS, external anal sphincter; IAS, internal anal sphincter

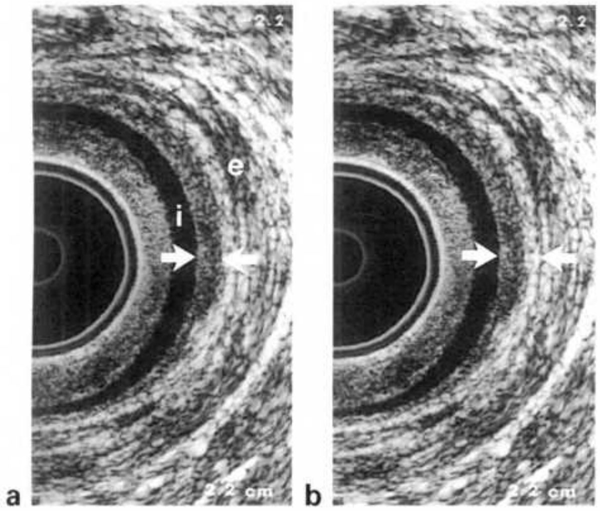

Fig. 1 Longitudinal muscle thickness (between arrows) measured at mid anal canal level by **a** observer 1 (2·0 mm) and **b** observer 2 (3·0 mm). The internal sphincter (i) is the hypoechogenic ring medial to the longitudinal muscle and the external sphincter (e) is the mixed echogenicity ring lateral to the longitudinal muscle

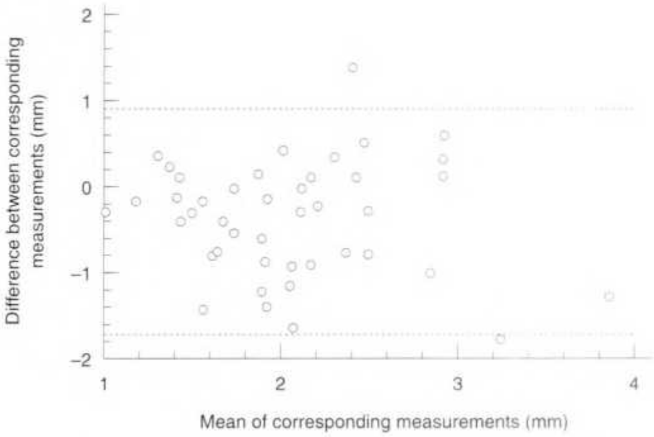

Fig. 2 Bland and Altman plot for longitudinal muscle thickness measured by two different observers at mid anal canal level. The limits of agreement are from −1·7 mm to 0·9 mm, contained by the two horizontal lines

Continuous data

The mean differences and limits of agreement for corresponding intraobserver and interobserver measurements of anal canal morphology are detailed in *Table 3*. The limits of agreement define the range of values that will encompass the 'true' value on 95 per cent of occasions[17]. An example of the observers' assessment of longitudinal muscle measurements at mid anal canal level is shown in *Fig. 1*, with the corresponding Bland and Altman plot shown in *Fig. 2*.

Discussion

Since its introduction, AES has become the examination of choice for the investigation of faecal incontinence, based on its ability to diagnose sphincter tears[3], abnormal thinning[4] or defects following surgery[19]. Although sonographic sphincter anatomy has been validated by several studies[20–22], surprisingly little work has been done relating to interobserver and intraobserver agreement. Error and variation in image interpretation has been described as radiology's 'Achilles' heel' because the human eye and brain have failed to keep pace with technological advances[23]; in many instances any difference between techniques is outweighed by the difference between observers. Nielsen and co-workers[11] assessed interobserver reproducibility of internal and external sphincter thickness in ten healthy volunteers. To the present authors' knowledge only one study has directly addressed the problem of reproducibility in AES[24], again using asymptomatic volunteers. Unfortunately, correlation and grand means were used to assess reproducibility, approaches that have been criticized statistically as correlation is a measure of linear association not agreement[17]. For example, this study found poor agreement for interobserver measurements of the mid anal canal EAS, even though correlation was highly significant ($r = 0{\cdot}85$, $P < 0{\cdot}0001$, Pearson correlation coefficient). Also, it cannot be assumed that two sets of measurements agree because hypothesis testing reveals no significant difference: information about average measurements is given but individual variation is ignored. Indeed, greater measurement error actually increases the chance that observers will appear to agree because of increased scatter around the mean[25].

The present study used appropriate statistical analysis to assess intraobserver and interobserver agreement between observations of structural abnormality and morphological measurements in a group of consecutive patients attending for routine anal sphincter examination. Examinations were digitized and reviewed using a personal computer so that both observers were studying exactly the same examination. Disagreement therefore relates primarily to uncertainty regarding interpretation of the various ultrasonographic interfaces and is probably most influenced by variability in echotexture. For example, the IAS is easily identified because its hypoechogenic nature highlights it against adjacent tissues. In contrast, the EAS is more difficult to define because of an echogenicity similar to that of the longitudinal muscle medially and ischioanal fat laterally, which is compounded by interface artefact due to the annular rotation of the transducer. Also it is not possible to locate measurements precisely in the longitudinal plane with AES, so that repeated measurements may be made at slightly differing levels. Discrepancies may also be due to the differing specialties of the sonographers, one of whom was a surgeon (D.M.G.) and the other a radiologist (S.H.); the latter was also familiar with endoanal magnetic resonance imaging, where the EAS may be delineated more clearly[26]. There is controversy concerning who should perform AES; radiologists are intensively trained in ultrasonographic technique and interpretation but surgeons will be more familiar with anal canal anatomy. This study concentrated primarily on variation in interpretation of the ultrasonographic image but it is likely that further variability would be introduced if individuals were repeatedly examined by the same or different sonographers, possibly with further variation between centres.

Unsurprisingly, there was better intraobserver than interobserver agreement for the morphological measurements made. Even then, repeated measurements of a relatively large structure such as the subcutaneous EAS could differ by over 5 mm (worst limits of agreement from −2·6 mm to +2·5 mm) and by over 1·4 mm for a smaller, better defined, structure such as the IAS in the mid anal canal (worst limits of agreement −0·7 mm to +0·8 mm). Interobserver agreement was poorest for measurements of anal striated muscle, with limits of agreement generally spanning over 5 mm. Internal sphincter measurements showed better agreement, with limits within 1·5 mm at all sites. Statistical analysis cannot be used to define acceptable limits of agreement, which is a clinical judgement[17,25], and it could be argued that differences in the order of millimetres are clinically acceptable.

There is considerable confusion when morphological anal canal measurements are correlated with physiological performance. For example, some investigators have found a relationship between sphincter size and performance[13,15,27], whereas others have not[10–12,14]. Failure to demonstrate a relationship may be because measurements are inaccurate[24], for example combining the longitudinal muscle and external sphincter together, or because no relationship exists. However, sphincter thickness is unequivocally increased[6] and decreased[4] in certain circumstances, demonstrating that measurements have diagnostic relevance even if this cannot be directly related to tests of physiological function. No debate exists with AES findings of sphincter tears since several studies have established a clear association between sonographic evidence of sphincter disruption and impaired physiological performance[3,9,21,27].

An additional aim of this study was to determine interobserver agreement with respect to the diagnosis of EAS and IAS tears, and overall agreement between assessors was found to be 'very good'[18] (weighted κ statistic of 0·80). Although there was no disagreement with respect to combined or isolated IAS tears, there was some disagreement regarding isolated EAS tears. Again this probably relates to difficulties with defining the sonographic boundaries of this muscle precisely. Internal sphincter defects are easiest to see on ultrasonography and, if present after obstetric injury, are almost always seen in combination with an EAS defect. Because of this, the presence of an IAS injury directs the sonographer towards an accompanying EAS defect, facilitating diagnosis of combined tears. 'Good' agreement[18] was reached for assessment of IAS echotexture. Increased IAS echogenicity suggests sphincter degeneration, especially if combined with muscle thinning[4].

In conclusion, this study has determined the limits of agreement for intraobserver and interobserver measurements of anal canal structures on AES and has additionally shown very good interobserver agreement for the diagnosis of sphincter trauma and features of IAS degeneration. Three-dimensional AES has recently been reported[28] and the ability to make measurements in the longitudinal plane, as well as estimates of sphincter volume, may eliminate some variability in conventional axial measurements in the future.

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Rectal examination in paediatric surgical practice

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Introduction

'If you don't put your finger in it, you risk putting your foot in it.'[1]

'You should never omit the rectal examination from your routine examination.'[2]

'The abdominal examination is not complete without the performance of a rectal examination.'[3]

Such phrases are deeply ingrained in medical teaching and give the impression that a rectal examination is an obligatory part of surgical clinical assessment. Documentation of a rectal examination has been used as an indicator of a thorough physical examination[4]. A normal rectal examination has been described among the required discharge criteria for children following appendicectomy[5].

The following article argues that in children rectal examination is a specialist investigation and should only be performed in certain limited situations. The evidence offered for this includes a comparison of the characteristics of rectal examination with those of an ideal investigation, a review of the possible indications and consideration of who should perform a rectal examination when required.

Rectal examination as an investigation

An ideal investigation should be safe, easy to learn and perform, cheap, non-invasive, reliable and contribute useful information. While usually considered safe[6], cheap and easy to learn, rectal examination may be traumatic and poorly tolerated in children who may not have the capacity to understand or consent to the procedure. Rectal examination may irreparably damage the bond of trust and cooperation that is vital to the clinical assessment and management of a child. In their prospective study of rectal examination in children aged less than 14 years with suspected appendicitis, Dickson and MacKinlay[7] classified the discomfort experienced as severe (major crying or screaming) or mild (minor crying or facial grimacing). Of 328 attempts at rectal examination it proved impossible on five occasions, provoked severe discomfort on 80 (24 per cent) and mild discomfort on 121 occasions (37 per cent). In encopretic children, Rockney *et al.*[8] highlighted the emotional disturbance associated with attempted rectal examination, particularly in victims of sexual abuse. In adults, the importance of adequate explanation was demonstrated by Ng *et al.*[9] in their survey of patients undergoing both rectal examination and rigid sigmoidoscopy; 80 per cent felt the need for detailed explanation before the procedure.

Rectal examination often yields information of limited usefulness. Dickson and MacKinlay[7] elicited 'positive' findings in 61 of 103 preoperative examinations (55 tenderness, six swelling) in patients with histologically proven appendicitis. In children without appendicitis (operated and non-operated) 12 of 98 had rectal tenderness (one had salpingitis). The authors reported that in only two patients did rectal examination alter management. The interpretation of 'tenderness' may be difficult given the discomfort associated with rectal examination. The diagnosis of acute appendicitis can be made in over 90 per cent of patients from the history and abdominal examination alone. Bonello and Abrams[10] reported similar results in a retrospective study of patients who needed appendicectomy. Of 95 children under 12 years old, 87 had appendicitis, 45 per cent of whom had a 'negative' rectal examination. Of the eight children who did not have appendicitis, two had a 'positive' examination.

In a study of minor rectal bleeding in children up to 14 years old rectal polyps were diagnosed after sigmoidoscopy under general anaesthesia in 53 per cent. Of these, 34 per cent were not diagnosed by rectal examination alone[11]. A series examining children (mean age 77 months) with colonic polyps found only 16 of 77 patients in whom the polyps were palpable on rectal examination[12].

Harrington *et al.*[13] studied clinical predictors for intussusception and found a positive predictive value of 93 per cent for the triad of intermittent abdominal pain, vomiting and a right upper quadrant abdominal mass. The additional finding of gross or occult blood on rectal examination did not then alter management.

The information gained from rectal examination may often be obtained or improved upon by other means, such as general examination, radiology or examination under anaesthesia. The studies quoted above regarding rectal examination in suspected acute appendicitis predate the widespread adoption of ultrasonography in paediatric surgical practice[14]. A study of ultrasonography in the diagnosis of intussusception[13] found it had a sensitivity and specificity both exceeding 95 per cent. In a study of minor rectal bleeding in children[11], all patients underwent examination under anaesthesia and sigmoidoscopy. Rectal examination of a conscious child was therefore unnecessary.

Indications for rectal examination in children

By considering rectal examination as an investigation rather than as a routine part of clinical examination its side-effects, acceptability, sensitivity and specificity in various conditions can be compared with alternative investigations so a rational decision can be made on when it is indicated.

In general, investigations are indicated when it is expected that the results will facilitate, or alter, either actual or anticipated management. Rectal examination in children is used primarily for diagnosis. The principal indications are as follows: acute abdomen, trauma, gastrointestinal bleeding, suspected abnormal neurology (e.g. spinal or presacral lesion[15]), chronic gastrointestinal symptoms (e.g. pain, failure to thrive) or congenital anomaly.

In practice even these situations rarely necessitate rectal examination in a conscious child. Of 1140 children aged less than 12 years presenting with acute abdominal pain to an American teaching hospital, only 56 had a documented rectal examination[16]. 'Clinically contributory findings' were obtained in only 12 patients with a diagnosis of constipation (five patients), gastroenteritis (three), appendicitis (two), adhesions (one) and non-specific abdominal pain (one). Given the high incidence of self-limiting, non-specific acute abdominal pain encountered in children, instructions to perform a rectal examination in all patients would mean a huge number of unnecessary, possibly traumatic interventions. At Sheffield Children's Hospital routine assessment of the child with acute abdominal pain involves clinical examination (without rectal examination) followed by a period of 'active observation' in equivocal cases. Should the clinical features remain equivocal over time, ultrasonography and/or other radiology may be indicated. Central to this is the concept of 'active observation'[17,18] which reduces the number of negative laparotomies[19] and obviates the need for routine rectal examination.

The value of rectal examination after trauma in children is less certain. This is clearly seen in the guidance given in the Advanced Paediatric Life Support (APLS)[20] and Advanced Trauma Life Support (ATLS)[21] manuals, respectively. While ATLS states that rectal examination is an essential part of trauma assessment, APLS recommends that a rectal examination be carried out only by an experienced surgeon caring for the child and only if the result will alter management.

The importance of a properly performed rectal examination has been emphasized in the assessment of suspected sacrococcygeal teratoma. Malone *et al.*[15] described two patients in whom failure to assess the presacral space delayed the diagnosis.

Who should perform the examination?

Rectal examination in children should only be undertaken on the instruction of senior trained personnel. A clinician of sufficient experience should actually perform the rectal examination. This will improve the information obtained and avoid basic errors and unnecessary repetition, which have been described in a number of reports[7,10,16]. With parental consent, and the child's, if practical, the teaching of proper technique can be undertaken during a general anaesthetic. Hennigan *et al.*[22] demonstrated that rectal examinations on anaesthetized adult patients significantly increased the confidence of medical students in their ability to diagnose rectal conditions.

Conclusion

The use of rectal examination in children is not straightforward. Surgical dogma urges doctors to avoid errors of omission whilst ignoring errors of commission. Traditional teaching on the role of rectal examination needs reappraisal and revision. In children, rectal examination has potential adverse effects and is indicated only when findings are expected to change management. On the rare occasions it is merited, rectal examination should be performed by an experienced clinician.

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Changing strategy for rectal cancer is associated with improved outcome

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Background: In 1980, surgery for rectal cancer at the Department of Surgery, Uppsala University Hospital was concentrated to a colorectal unit and a more systematic use of adjuvant radiotherapy began. In 1985, total mesorectal excision was introduced. The aim of this study was to determine whether these changes had an impact on the overall treatment outcome.

Methods: Some 423 consecutive patients with rectal cancer had surgery between 1974 and 1995 and were followed up until 1 January 1998. Outcome analysis was made according to the following predefined intervals of diagnosis: 1974–1979, 1980–1984 and 1985–1995.

Results: The overall local recurrence rate was 47 per cent in the first interval, and 13 and 11 per cent during the second and third respectively ($P < 0.001$). In the third interval, of 119 patients who received preoperative irradiation and underwent radical resection, only three (3 per cent) had locally recurrent rectal cancer. There was improved cancer-specific survival between the first and the last intervals of the study ($P = 0.03$).

Conclusion: These data are consistent with the interpretation that the results of treatment can be improved by concentration of surgery to a colorectal team.

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Introduction

Local recurrence after surgery for rectal cancer differs markedly among patient series, varying from less than 10 per cent[1] to as much as 65 per cent[2]. Although this difference is often difficult to interpret, some of the reasons for the variation may involve patient selection, different definitions of curative surgery, surgical skill and different follow-up routines. With the new surgical techniques of total mesorectal excision (TME)[1] and extended lymphadenectomy[3], it has been asserted that local recurrence rates can be reduced to below 10 per cent. Long-term survival may be improved as a result of these procedures. However, the average local failure rate is 29 per cent[4] when 'standard' surgery has been compared with radiotherapy. Because no controlled trials have been performed, comparisons between surgical techniques are mainly based on historical controls.

Additional treatments, such as radiotherapy and chemotherapy, were long believed to have no beneficial effect on survival. More recently, a number of controlled trials have indicated that not only local recurrence rates but also survival from rectal cancer may be improved by one, or a combination, of these two therapeutic modalities[4]. The survival benefits are still relatively small but, since rectal cancer is a common disease, small improvements in outcome will affect many individuals.

In Sweden, the treatment of rectal cancer used to be the responsibility of the general surgeon and, in most cases, adjuvant therapy was not considered necessary. In 1980, two major alterations in the primary treatment of rectal cancer occurred at the University Hospital in Uppsala. Rectal surgery was concentrated to a colorectal unit and systematic use of adjuvant radiotherapy was initiated. In 1985, TME was introduced.

The aim of the present study was to determine whether these changes in the primary treatment for rectal cancer have had a significant impact on local recurrence rates and survival in a consecutive single-unit series.

Patients and methods

Patients

Between 1974 and 1995, 531 consecutive patients had invasive rectal cancer diagnosed. Of these, 423 patients had surgery and were included for later analysis. Nineteen patients died after operation and were not included. Some 89 patients did not undergo resection because of severe generalized disease (33 patients), irresectable tumours (39), deteriorating physical condition (13) or because they refused treatment (four).

Follow-up (in most cases prospectively) of all patients was performed until 1 January 1998. Patients included in the follow-up were divided into three groups according to predefined intervals of diagnosis: 1974–1979, 1980–1984 and 1985–1995.

The primary catchment area has enlarged during the study. In addition, referrals of patients with locally advanced tumours from outside the catchment area have increased, especially during the third interval (1985–1995). The number of referrals was 2, 5 and 17 respectively for each interval. The mean number of patients per annum who underwent resection for each interval was 13, 17 and 24 respectively.

Surgical technique

Standard surgical techniques were applied before the change to TME in 1985. With the introduction of TME, a strict application of total removal of the whole length of the mesorectum for upper-third rectal tumours was not applied; in these patients, the mesorectum was divided horizontally at least 5 cm below the tumour.

Operations during the first interval were evenly distributed among 12 senior surgeons; most did not have a specific colorectal interest. In the second interval, 63 (73 per cent) of 86 operations were performed by five colorectal surgeons, one of whom performed or assisted in 58 operations (67 per cent). In the last interval, 242 (93 per cent) of 260 operations were done by eight colorectal surgeons, three of whom employed the TME technique in 198 (76 per cent) of the 260 patients.

Irresectable tumours that could not be removed at laparotomy were excluded from the analysis. Operable tumours were classified as mobile (T_1–T_3 tumours) or locally advanced (T_4 lesions according to the preoperative clinical examination, i.e. immobile tumours with fixation to pelvic organs except the vagina and large bulky tumours that were not mobile).

Adjuvant treatment

Radiotherapy

After a pilot phase[5] to evaluate preoperative radiotherapy using five sessions of 5 Gy and a randomized trial[6] from 1980 to 1985 comparing this preoperative regimen with postoperative radiotherapy (30 sessions of 2 Gy), it was recommended that all patients, except those with small polypoid tumours, be given preoperative radiotherapy. However, between 1987 and 1990 the Swedish Rectal Cancer Trial[7] was conducted which randomized patients between surgery alone and surgery after preoperative radiotherapy (five sessions of 5 Gy). Endoscopic ultrasonography was used to exclude patients with a tumour that appeared to be limited to the bowel wall[8].

Patients with locally advanced tumours had preoperative radiotherapy alone (2–46 Gy) or radiotherapy 2–40 Gy split course, plus chemotherapy[9].

Chemotherapy

Adjuvant chemotherapy has been used since May 1993 in a randomized study for Dukes B and C rectal cancers. Nine patients received adjuvant chemotherapy. Palliative chemotherapy has been provided since 1985 within several randomized trials[10,11].

Statistical analysis

Differences in proportions were calculated using the χ^2 test. Statistical significance was accepted at $P \leq 0{\cdot}05$. Survival and local recurrence rates were analysed with the log rank test. Analyses of postoperative death were based on all patients who underwent resection, whereas patients who died within 30 days of surgery were excluded from analyses of survival and local recurrence. Local recurrence was defined as recurrent tumour growth within the pelvis and below the pelvic brim. Local recurrence was recorded, regardless of whether distant metastases were evident, in all patients in whom the tumour-bearing bowel segment had been resected.

Results

There was no significant change in patient age or sex ratio during the study. The tumour height from the anal verge was slightly decreased in the last interval, and the choice of surgical procedure shifted towards anterior resection. There were more locally advanced tumours undergoing resection during the final diagnostic interval (*Table 1*).

Table 1 Patient characteristics in the study population

	1974–1979 (n = 77)	1980–1984 (n = 86)	1985–1995 (n = 260)	P†
Sex ratio (M : F)	47 : 30	45 : 41	151 : 109	n.s.
Age (years)*	70 (39–91)	69 (37–90)	70 (29–93)	n.s.
Tumour height from anal verge (cm)*	10 (1–15)	10 (1–15)	7 (0–15)	< 0·005‡
Pretreatment evaluation				
Mobile, no metastasis	68 (88) } (94)	77 (90) } (93)	206 (79) } (84)	n.s.
Mobile, metastasis	5 (6)	3 (3)	12 (5)	
Locally advanced, no metastasis	4 (5) } (5)	5 (6) } (7)	35 (13) } (16)	< 0·01‡
Locally advanced, metastasis	0	1 (1)	7 (3)	
Surgical procedure				
Anterior resection	20 (26)	47 (55)	154 (59)	0·002§
Abdominoperineal excision	53 (69)	36 (42)	88 (34)	0·001§
Other	4 (5)	3 (3)	18 (7)	
Adjuvant radiotherapy	15 (19)	66 (77)	167 (64)	< 0·001§
Preoperative 25 Gy	8 (10)	39 (45)	120 (46)	
Preoperative > 25 Gy	3 (4)	6 (7)	40 (15)	
Postoperative	4 (5)	21 (24)	7 (3)	

Values in parentheses are percentages except *values are median (range) †χ^2 test or Mann–Whitney U test. ‡The last interval compared with the first two, §the last two intervals compared with the first

Table 2 Local recurrence rates overall and by Dukes stage and diagnostic interval

	1974–1979					1980–1984					1985–1995				
	A	B	C	D	Total	A	B	C	D	Total	A	B	C	D	Total
Mobile tumours															
Locally curative	6/22	11/25	8/14	4/7	29/68 (43)	1/18	4/26	4/24	1/9	10/77 (13)	4/51	4/73	7/63	3/20	18/207 (9)
No irradiation	5/20	10/20	8/14	4/6	27/60 (45)	1/10	0/5	0/1	0/4	1/20 (5)	4/30	4/26	3/19	1/8	12/83 (14)
Preop irradiation	1/2	0/4	–	0/1	1/7 (14)	0/8	3/16	1/10	1/4	5/38 (13)	0/21	0/45	3/43	0/10	3/119 (3)
Postop. irradiation	–	1/1	–	–	1/1	–	1/5	3/13	0/1	4/19 (21)	–	0/2	1/1	2/2	3/5 (60)
Locally not curative	1/1	3/3	1/1	–	5/5	–	–	0/1	0/2	0/3 (0)	2/2	0/3	0/1	2/5	4/11 (36)
Overall	7/23	14/28	9/15	4/7	34/73 (47)	1/18	4/26	4/25	1/11	10/80 (12)	6/53	4/76	7/64	5/25	22/218 (10)
Locally advanced tumours															
Locally curative	–	2/2	0/2	–	2/4	–	1/4	0/1	–	1/5	–	2/14	2/13	0/8	4/35 (11)
Locally not curative	–	–	–	–	–	–	0/1	–	–	0/1	–	2/3	1/2	1/2	4/7 (57)
Overall	–	2/2	0/2	–	2/4	–	1/5	0/1	–	1/6	–	4/17	3/15	1/10	8/42(19)
Total	7/23	16/30	9/17	4/7	36/77 (47)	1/18	5/31	4/26	1/11	11/86 (13)	6/53	8/93	10/79	6/35	30/260 (12)

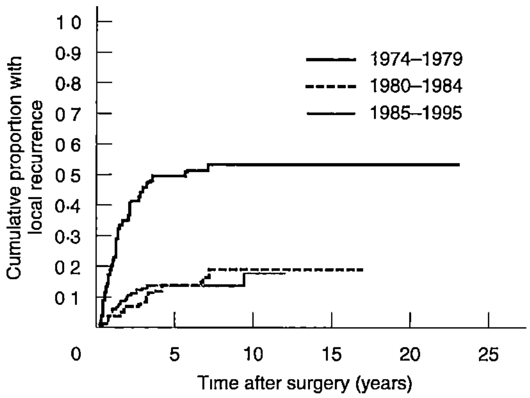
Values in parentheses are percentages

According to the Dukes system, stage distribution did not differ significantly between diagnostic intervals (*Table 2*). The proportion of patients who had a resection increased from 76 per cent in the first interval to 77 and 90 per cent in the second and third intervals respectively (P = 0·34).

The postoperative in-hospital mortality rate was 9 per cent (eight of 85) for 1974–1979; for the following two intervals it was 5 per cent (five of 91) and 2 per cent (six of 266) respectively (P = 0·01).

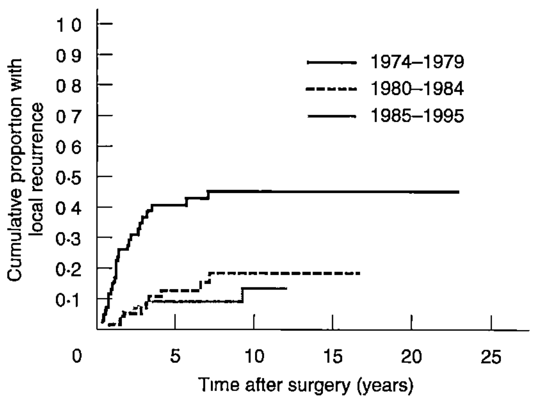
Local recurrence

The local recurrence rates declined markedly between the first (47 per cent; 36 of 77) and second (13 per cent; 11 of 86) (P < 0·001) intervals, but for the third interval there was no further overall reduction (12 per cent; 30 of 260). A similar pattern was found among patients with mobile tumours undergoing curative surgery (*Table 2*, *Figs 1* and *2*). However, in the last interval, the local failure rate was reduced to 3 per cent (three of 119) (P < 0·05) for the large subgroup of patients with mobile tumours that received preoperative irradiation. More local recurrences (14 per cent; 12 of 83) (P = 0·006) were noted among patients who did not have radiotherapy, even if the distribution according to Dukes stage was more favourable (*Table 2*). When stratifying the last 10 years into two separate intervals (i.e. 1985–1989 and 1990–1995), there was a further reduction in local recurrence rates for patients



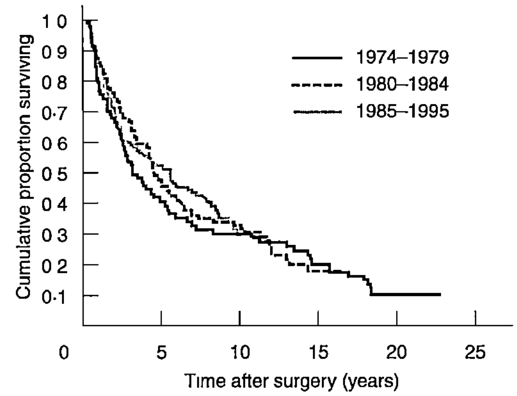
No at risk						
1974–1979	77	28	22	15	4	0
1980–1984	86	39	27	4	0	0
1985–1995	260	66	10	0	0	0

Fig. 1 Cumulative local recurrence rate among all patients who had a resection for rectal cancer



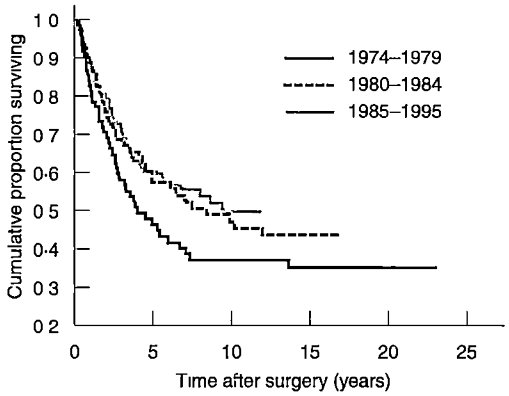
No at risk						
1974–1979	61	28	22	15	4	0
1980–1984	68	37	25	4	0	0
1985–1995	185	62	9	0	0	0

Fig. 2 Cumulative local recurrence rate among patients with resectable tumours undergoing curative surgery



No. at risk						
1974–1979	77	31	22	15	4	0
1980–1984	86	39	27	4	0	0
1985–1995	260	69	10	0	0	0

Fig. 3 Cumulative overall survival among all patients who had a resection for rectal cancer



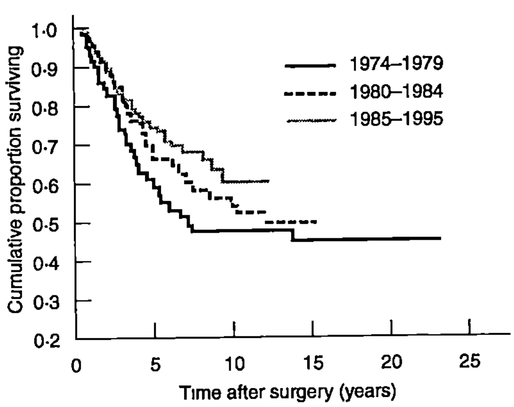
No. at risk						
1974–1979	77	31	22	15	4	0
1980–1984	86	39	27	4	0	0
1985–1995	260	69	10	0	0	0

Fig. 4 Cumulative cancer-specific survival among patients who had a resection for rectal cancer

Table 3 Local recurrence rates for mobile tumours by surgical procedure and diagnostic interval

	1974–1979			1980–1984			1985–1995		
Mobile tumours	AR	APR	Other	AR	APR	Other	AR	APR	Other
Locally curative	6/18	23/47	0/3	3/44	7/31	0/2	8/127	9/70	0/10
No irradiation	6/14	21/43	0/3	0/12	1/6	0/2	6/49	5/27	0/7
Preop. irradiation	0/4	1/3	–	1/19	4/19	–	0/74	3/42	0/3
Postop irrad	–	1/1	–	2/13	2/6	–	2/4	1/1	–
Locally not curative	–	4/4	1/1	0/1	0/1	0/1	2/5	0/1	2/5
Overall	6/18 (33)	27/51 (53)	1/4 (25)	3/45 (7)	7/32 (22)	0/3	10/132 (8)	9/71 (13)	2/15 (13)

Values in parentheses are percentages. AR, anterior resection; APR, abdominoperineal excision of the rectum



No. at risk	0	5	10	15	20	25
1974–1979	61	31	22	15	4	0
1980–1984	68	37	25	4	0	0
1985–1995	187	65	9	0	0	0

Fig. 5 Cumulative cancer-specific survival among patients with resectable tumours who underwent curative surgery

with mobile curatively resected tumours from 14 per cent (12 of 85) to 5 per cent (six of 122) ($P = 0{\cdot}05$). Throughout the study results were better in patients who had anterior resection rather than abdominoperineal excision of the rectum (*Table 3*). The local failure rates after anterior resection for tumours above 10 cm were six of 17, three of 30 and two of 47 for the first, second and third intervals respectively ($P = 0{\cdot}017$). The corresponding figures following abdominoperineal resection for tumours below 6 cm were 10 of 18, five of 17 and seven of 66 respectively ($P = 0{\cdot}007$). The choice of surgical procedure with regard to tumour height did not change during the study.

Survival

Although there was a trend towards improved overall survival in the comparison between the first and third intervals, the difference was not significant ($P = 0{\cdot}27$, *Fig. 3*). The overall 5-year survival rates for each interval were 40 (95 per cent confidence interval 29–50), 44 (34–54) and 51 (45–58) per cent respectively. However, the difference in cancer-specific survival among all patients who had a resection and among patients with mobile tumours undergoing curative surgery was significant in comparisons involving the first and third intervals ($P = 0{\cdot}03$ and 0·01 respectively, *Figs 4* and *5*).

Discussion

This study indicates that changing the strategy in the primary treatment of rectal cancer was associated with improved outcome. Over the study intervals there was a marked decline in overall local recurrence rates (from 47 to 12 per cent) and an improved cancer-specific survival. This improvement occurred when all rectal cancer surgery was concentrated to a colorectal unit and additional radiotherapy was increasingly used. Between the second and third intervals there was a trend to improved cancer-specific and overall survival while no reduction in overall local failure rates was seen.

Concentrating the surgery to a subspecialized unit with an increase in volume, interest and knowledge of the individual surgeon is likely to yield a higher degree of achievement to the principles of good oncological surgery. There are also indications that the treatment outcome will further benefit from TME, as indicated when comparing local recurrence rates in the last two intervals for patients with tumours above 10 cm or below 6 cm from the anal verge. The shift towards anterior resection has not affected tumours at these levels, which would reduce one confounding factor. Additionally, by dividing the last 10 years into two intervals, a further reduction in local recurrence rates was observed, possibly as a consequence of continued refinement of the TME technique. The lack of overall reduction in local failure rates after the introduction of TME in 1985 has several possible explanations. One is a changed referral pattern with a subsequent increase in resection of locally advanced tumours. Another is a more selective use of radiotherapy although some patients were randomized to no radiotherapy.

The systematic use of adjuvant radiotherapy was also initiated in 1980. Both preoperative and postoperative radiotherapy reduced local recurrence rates[7,12–15], although preoperative irradiation did this more effectively[16]. Furthermore, in recent studies preoperative radiotherapy has not only reduced local recurrence rates by more than half[7,12–14] but also improved survival[7,15].

The effectiveness of the combination of preoperative irradiation and TME is shown in the last interval by a low local recurrence rate (3 per cent) for the large subgroup of patients who underwent elective TME for mobile, preoperatively irradiated tumours. This combination is the authors' current treatment of choice for most patients with primary rectal cancer. Further support for this view is the improved survival rate in patients (on a population level) with rectal cancer during the 1985–1989 interval in the county of Uppsala compared with the rest of Sweden[17]. During this interval, the University Hospital in Uppsala was the only centre in Sweden in which this combined treatment was used systematically.

Other factors that may influence outcome are improved diagnostic techniques, screening programmes and changed socioeconomic status. None of these factors offers a plausible explanation for the results of the present study.

Rather, there has been an increase in resection of advanced tumours. To date, no screening programme has been established.

This study suggests that treatment of cancer of the rectum can be improved by the concentration of rectal cancer surgery to a colorectal unit. Adjuvant preoperative irradiation and the refinement of surgical technique to a procedure such as TME may improve outcome further.

Acknowledgements

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Surgical implications of underestimation of adrenal tumour size by computed tomography

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Background: Size of adrenal mass is an important consideration during adrenal surgery, with regard to the choice of surgical approach and management of adrenaloma. The aim of the present study was to evaluate the precision of preoperative computed tomography (CT) on the size estimation of adrenal lesions and to review its potential implications on surgical decision making.

Methods: Records of 110 patients who underwent adrenalectomy for various adrenal pathologies from 1981 to 1997 were reviewed retrospectively. Patients ($n = 92$) who had documented dimensions of adrenal mass by both preoperative CT and pathological examination were selected for analysis.

Results: CT overall underestimated the actual size of adrenal lesions by 16 per cent compared with measurement of resected specimens (mean 3·1 *versus* 3·6 cm; $P < 0·001$). There was a significant underestimation of the actual size of adrenal lesions measuring less than 6 cm by CT but not for lesions larger than 6·0 cm. Phaeochromocytoma ($n = 17$) was the only pathological condition consistently underestimated by CT.

Conclusion: Conventional CT overall underestimates the real size of adrenal lesions, in particular phaeochromocytoma and adrenal tumours of less than 6·0 cm in size. Surgical decision making based on size should take this limitation into account.

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Introduction

Computed tomography (CT) is by far the most commonly employed imaging modality for localizing and estimating the size of adrenal lesions. Because of the low incidence of malignancy in small adrenal tumours, adrenaloma size has been regarded as one of the most important criteria for deciding in favour of surgical resection[1,2]. The size of adrenal lesions is also an important consideration in the surgeon's decision about the surgical approach to be used for a particular adrenal tumour[3]. The aim of the present study was to assess the precision of preoperative CT in estimating the size of adrenal lesions. Its potential impact on surgical decision making was evaluated.

Patients and methods

From 1981 to 1997, records of 110 patients who underwent adrenalectomy for various adrenal lesions were reviewed retrospectively. Patients who had documented dimensions of the adrenal lesions from preoperative CT within 8 weeks before surgery and from resected specimens before pathological examination ($n = 92$) were selected for analysis.

Axial CT of adrenal glands was performed with a section thickness ranging from 3 to 5 mm contiguous intervals. The same scanner (GE 9800 system; General Electric Medical Systems, Milwaukee, Wisconsin, USA) was used throughout the study. The maximal transverse diameter of the adrenal tumour on the scan was measured by adjustable markers on the computer screen and recorded by experienced radiologists, whereas actual tumour size was measured by the pathologist to the nearest millimetre in formalin-fixed specimens. There were 33 men and 59 women with ages ranging from 15 to 83 (median 47) years.

Pathological conditions included aldosteronoma ($n = 54$), phaeochromocytoma ($n = 17$), Cushing's syndrome ($n = 9$), non-functioning lesions ($n = 9$) and adrenocortical carcinoma ($n = 3$). Non-functioning lesions included ganglioneuroma in three, cortical adenoma in two, myelolipoma in two, and adrenal cyst and metastasis from a non-adrenal primary in one patient each. The traditional open operative procedures included posterior lumbar in 46, anterior transabdominal in 22 and flank extraperitoneal in eight patients. Since 1995, 16 patients underwent an attempted lateral transperitoneal laparoscopic approach, of whom two required conversion to open operation.

The maximal dimension of adrenal lesions reported at preoperative CT was compared with that measured at pathological examination. The tumours were then divided into three groups: group 1, tumour size 3·0 cm or less; group 2, 3·1–6·0 cm; and group 3, 6·1 cm or more, based on the size estimated at CT. Comparison was performed with respect to individual size subgroup and tumour pathology.

Data were collected retrospectively and analysed, with all values expressed as mean(s.e.m.). Statistical analysis was performed with the help of computer software (SPSS/PC+ 7·0, SPSS, Chicago, Illinois, USA). A paired-samples t test was used to compare continuous variables. $P < 0·05$ was regarded as statistically significant.

Results

Overall analysis

CT overall underestimated the actual size of adrenal lesions. The mean(s.e.m.) tumour size estimated by CT and during pathological examination was 3·1(0·3) and 3·6(0·4) cm respectively ($P < 0·001$). The actual tumour size was 16 per cent larger than the value estimated by CT.

Size subgroup analysis

Comparison between the estimated and actual tumour size according to the three subgroups is shown in *Table 1*.

Table 1 Comparison of tumour size estimated by computed tomography and actual tumour size in each size subgroup

	Size (cm)	Percentage difference	P*
Group 1 0–3·0 cm (n = 65)		13	0·01
Estimated	1·6(0·1)		
Actual	1·8(0·1)		
Group 2: 3·1–6·0 cm (n = 17)		23	0·001
Estimated	4·8(0·2)		
Actual	5·9(0·4)		
Group 3: ≥ 6·1 cm (n = 10)		12	0·21
Estimated	10·1(1·3)		
Actual	11·3(1·8)		

Values are mean(s.e.m.). Groups are divided according to the maximal dimension estimated by computed tomography. *Paired-samples t test

There was a significant underestimation of the actual size of adrenal lesions when they were shown to be under 3·0 cm and between 3·1 and 6·0 cm by CT. Of the 82 patients with tumours measuring 6·0 cm or less diameter at CT, a mean discrepancy of 17 per cent was observed in the actual tumour size. In group 2 ($n = 17$) in which CT estimated a tumour size of between 3·1 and 6·0 cm, six adrenal lesions, including five phaeochromocytomas and one ganglioneuroma, turned out to have an actual size of larger than 6·0 cm (mean 7·8 cm).

Tumour pathology analysis

Comparison between the estimated and actual size according to individual tumour pathology is shown in *Table 2*. Phaeochromocytoma ($n = 17$) was the only pathological condition consistently underestimated by preoperative CT ($P = 0·02$). The tumour size of ten patients with phaeochromocytoma was underestimated by CT compared with that of pathological examination. All patients with primary adrenal carcinoma ($n = 3$) presented with tumours larger than 6·0 cm in size.

Laparoscopic conversion

Two patients required conversion from laparoscopic to open procedures. One patient had an adrenal schwannoma of 7 cm diameter, which was underestimated to be 5·6 cm by preoperative CT. Another patient had a benign phaeochromocytoma of 8 cm diameter, whose size was estimated accurately at preoperative CT.

Table 2 Comparison of tumour size estimated by computed tomography and actual tumour size according to individual tumour pathology

	Size (cm)	P*
Aldosteronoma (n = 54)		0·08
Estimated	1·4(0·1)	
Actual	1·6(0·1)	
Phaeochromocytoma (n = 17)		0·02
Estimated	5·1(0·5)	
Actual	6·0(0·5)	
Cushing's syndrome (n = 9)		0·09
Estimated	2·5(0·3)	
Actual	3·0(0·3)	
Non-functioning (n = 9)		0·33
Estimated	6·5(1·5)	
Actual	7·1(1·3)	
Carcinoma (n = 3)		0·16
Estimated	12·1(3·1)	
Actual	16·3(4·9)	

Values are mean(s.e.m.). *Paired-samples t test

Discussion

This study demonstrated the relative inaccuracy of conventional axial CT in evaluating the size of adrenal lesions, particularly for tumours measuring less than 6·0 cm in dimension and phaeochromocytoma. These results were consistent with those of previously reported series[4,5].

Conventional axial CT measures the transverse dimensions of an adrenal lesion alone. However, the growth of an adrenal tumour may occur in an oblique or craniocaudal direction. The maximal diameter of these non-spherical tumours does not uncommonly lie on the sagittal plane. This growth pattern is probably more predominant in adrenal medullary tumours than adrenocortical tumours. The frequent underestimation of the actual size of a phaeochromocytoma by CT was also partly attributed to the mean tumour diameter lying in the range 3·1–6·0 cm which was shown to be the most significantly underestimated size subgroup.

Shrinkage of tumour occurs invariably after fixation in 10 per cent formalin. The disparity between the CT result and the actual size should be more apparent once shrinkage of tumour after formalin fixation is taken into account.

Traditionally, the open posterior approach is generally not recommended for benign tumours larger than 5 cm in size because of operative field confinement[3,6]. The size limit of adrenal lesions feasible for a laparoscopic approach depends on the primary pathology and the availability of surgical expertise[7–9]. Accurate preoperative estimation of tumour size therefore allows an appropriate selection of surgical approach within the available surgical capacity. Frequent underestimation of the size of phaeochromocytoma by CT should be borne in mind to avoid unnecessary conversion when a laparoscopic approach is adopted.

The management of an incidentally discovered adrenal mass remains controversial. The recommended cut-off size for resection of adrenaloma varies from 3 to 6 cm in different series[10–12]. No universal consensus on an exact cut-off value has been agreed. All of these recommendations are based on the analysis of pathological data, rather than preoperative CT measurements, whereas surgical decision making is based on size estimation by CT. Underestimation of the tumour size by preoperative CT can lead to a delay in surgery for patients with early carcinoma.

Tumours of less than 6·0 cm diameter on CT had the greatest size discrepancy compared with the actual dimensions. In this group of patients, the size of more than half of the tumours was underestimated by a mean of 17 per cent. It may imply that a recommended cut-off value of 5 cm, based on pathological data, should be adjusted to 4 cm for values estimated by CT.

When conservative treatment is adopted for patients with adrenaloma, follow-up CT, which measures transverse dimensions only, can potentially miss the craniocaudal growth of a lesion until a late stage is reached. The baseline and follow-up surveillance imaging modality should be able to document all dimensions of the lesion in order to give an accurate assessment of the growth rate. Magnetic resonance imaging or spiral CT with three-dimensional reconstruction could provide a better estimation in this aspect and should be recommended[13,14].

These results show that underestimation of the size of adrenal lesions by conventional axial CT is common and should be borne in mind during surgical decision making.

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Effect of training on the incidence of nerve damage in thyroid surgery

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Background: In thyroid surgery early postoperative recurrent laryngeal nerve (RLN) dysfunction offers a sensitive measure of the quality of the operation. The aim of this study was to analyse the effect of training in thyroid surgery on the rate of early functional disturbances of the RLN after thyroid resection.

Methods: In 617 patients (median age 48 years, female to male ratio 2·8 : 1) who underwent unilateral or bilateral thyroid resection, 1059 RLNs were subjected to operative risk. Laryngoscopy was performed before and after operation. The 45 surgeons were divided into three groups: group 1, specialist thyroid surgeons; group 2, experienced surgeons; and group 3, residents. Personal gain of experience was defined by the preceding number of thyroid operations. Within each group the complication profile was determined by adding the personal complication profiles of each surgeon.

Results: The complication rates were low during surgical residency (group 3). In group 2 complication rates increased up to the 50th operation. Group 1 showed the expected exponential decrease to under 1 per cent after another 130 operations.

Conclusion: Complication rates are affected considerably by the extent of surgical experience in a non-linear and complex logarithmic manner, starting with low rates in the beginner group, peaking after further experience and then decreasing exponentially.

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Introduction

Some 2–3 per cent of all medicolegal claims in general surgery involve the consequences of thyroid surgery. Nearly exclusively these were related to injury to the recurrent laryngeal nerve (RLN)[1] (Schiedsstelle der Landesarztekammer Karlsruhe, Germany; personal communication). Data from the literature regarding the rate of postoperative functional disturbances of the RLN vary greatly. Large statistical series of over 12 000 documented thyroid resections have reported rates of the order of 1·2 per cent or 5·2 per cent of permanent RLN palsies depending on whether or not the nerve was exposed during surgery[2]. Because of the fine structure and varying course of the RLN, this procedure places particular demands on the surgeon[3–6]. Mechanical trauma caused by indirect tension on the nerve during mobilization of the thyroid or direct injury of the nerve during preparation causes functional disturbances of the target organ, the vocal cords.

Although these early functional disturbances are temporary in most cases (approximately 90 per cent have resolved within 1 year) they lead to significant morbidity weeks to months after operation and may have serious consequences in professions which depend on speech.

The aim of this study was to analyse the effect of training in thyroid surgery on the rate of early functional disturbances of the RLN after thyroid resection.

Patients and methods

In 617 patients who underwent unilateral or bilateral thyroid resections, 1059 RLNs were subjected to operative risk. The preoperative and intraoperative diagnosis was benign goitre. All patients undergoing reoperation were excluded. The data were analysed prospectively. The median age of these patients was 48 years. The female to male (F : M) ratio was 2·8 : 1. Bilateral thyroid resection was performed in 442 patients (median age 49 years, F : M ratio 3·1 : 1) and unilateral resection in 175 patients (median age 44 years, F : M ratio 2·2 : 1). The operations were carried out by 45 surgeons.

Individual experience in thyroid surgery

To assess the general surgical experience the surgeons were divided into three groups. Group 1 comprised two surgeons with many years of experience who during the study period were specializing in thyroid surgery. Group 2 ($n = 19$) comprised experienced surgeons who did not specialize in thyroid surgery. Group 3 ($n = 24$) consisted of physicians in surgical training (residency) who were assisted by experienced surgeons from group 2. The details of patients operated on by the three groups are shown in *Table 1*.

The individual experience at any time was determined by the number of all types of thyroid operations the individual surgeon had already performed at that time. All operations were indexed consecutively with a running number. In this way one could determine at which stage of individual experience in thyroid operations a complication took place. All operations which did not meet the inclusion criteria were then excluded without changing the index number. The individual rates of early functional disturbances of all surgeons within one group were superposed with respect to the index numbers and added. Within each group the operations were classified and the rates of early functional disturbance were calculated for the first five, next ten, next 15, next 20, next 50 and next 100 operations of experience, by dividing the number of observed complications by the number of nerves at risk.

Operative technique

The operative technique was standardized. Typical features of the operation were dissection of the straight neck muscles, ligation of the inferior thyroid artery, and exposure of the RLN over a distance of 1–2 cm avoiding extensive exposure. In fact, 1050 of the 1059 nerves at risk were definitely identified and exposed. In 21 patients the straight neck muscles were not dissected but held aside instead.

Table 1 Patients operated on by the three groups of surgeons

	Group 1	Group 2	Group 3
No. of patients	198	238	181
Nerves at risk	334	423	302
Mean (range) age (years)	48·8 (17–82)	49·3 (16–84)	45·2 (16–86)
M : F ratio	65 : 133	57 : 181	39 : 142
Nodular goitre	198	238	181

Laryngoscopy

All patients were examined before and after operation by a laryngoscopist (ear, nose and throat department). Any new functional disturbance of the RLN after surgery could be detected at this time. Early functional disturbances were diagnosed when reduced movement of a vocal cord was found within the first few days after operation (days 3–6). The first postoperative laryngoscopic examination was conducted in 94 per cent of all patients during days 3–5 and in all patients within 1 week after operation. Patients who were evaluated later were not included in the study.

Statistical analysis

Statistical analysis was conducted using Winstat (Kalmia, Cambridge, Massachusetts, USA) in cooperation with the institution of biomedical statistics of the University of Heidelberg.

Results

The total rate of early postoperative functional disturbances of the RLN with respect to the nerves at risk was 4·1 per cent (43 of 1059). No bilateral injuries were recorded. The rate of permanent RLN palsy after thyroid resection was 0·5 per cent (five of 1059) after 9 months. Thirty-eight of 43 early postoperative functional disturbances of the RLN were temporary.

The rates of early functional disturbance in the three groups are illustrated in *Fig. 1*. There were 11 cases in group 1 and nine in group 3. In group 2 the rate of early functional disturbance was nearly twice as high as that in group 1, with 23 nerves affected. There was no correlation

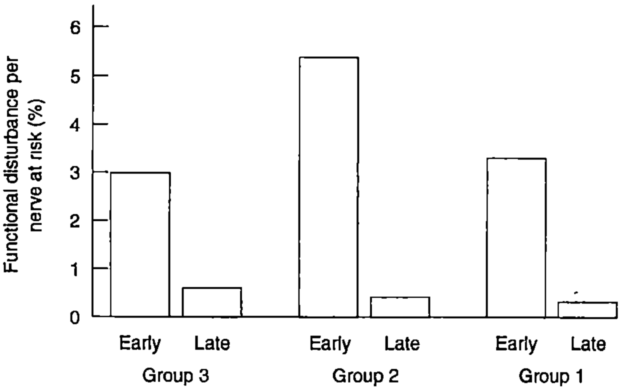

Fig. 1 Early and late functional disturbances per nerve at risk. The rate of early dysfunction was significantly higher ($P = 0·01$) in group 2 than in group 1. Permanent palsy rates (functional disturbances after 9 months) were similar in each group

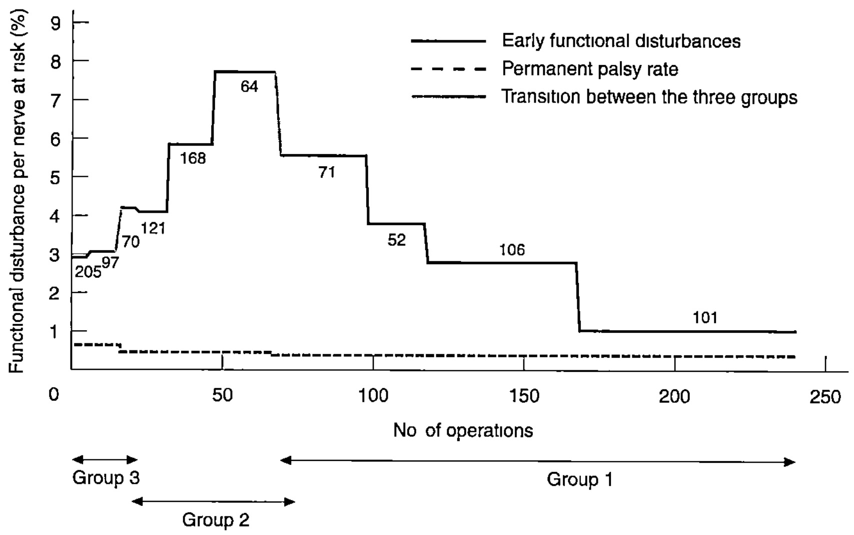

Fig. 2 Profile of early functional disturbances during various stages of the surgical maturation process from the beginner (group 3) to the advanced (group 2) and to the specializing (group 1). The x axis shows the cumulative number of operations as a measure of individual gain of experience. Values within the diagram are the number of nerves at risk. The first five operations in group 3 showed an early functional disturbance rate of 2 9 per cent. This rate increased within group 2 up to 7·8 per cent and decreased in group 1 to 1 per cent. In contrast the permanent palsy rate stayed low for all three groups.

between the extent of surgery and the rate of early functional disturbance or permanent RLN palsy.

Effect of individual increase in experience

Within each group, the operations were classified depending on the individual experience of the surgeon. The effect of the individual increase of experience within each group is demonstrated in *Fig. 2*. The first five operations in group 3 show a complication rate of 2·9 per cent which increases to 3·1 per cent in the course of the next ten operations. In group 2 the highest complication rate (7·8 per cent) is seen between 45 and 65 operations. Surgeons in group 1 start with a rate of 6 per cent for the first 30 operations which decreases exponentially to 1 per cent after another 80 operations.

Discussion

Early postoperative functional disturbances, which occur six to nine times more often than permanent RLN palsies, represent a sensitive measure of operative precision and quality. Although others have shown that residents can indeed perform thyroid operations safely they did not perform a detailed analysis[7].

In the present study the profile of early functional disturbance during various stages of the surgeon's training and increasing personal experience was analysed. At the time of a thyroid operation the experience of the surgeon was determined by the number of thyroid operations he or she had already performed. The complication rates for group 3 (surgical residency) were as good and sometimes even better than those of group 1 (specialists) (*Fig. 1*). Second operations, which are thought to carry a greater risk of complications, were excluded from the analysis. The good results of group 3 can be explained by a combination of conscientious preparation of the nerve by a careful beginner, and the routine and experience of a surgical mentor. They also show that the present selection criteria of patient/operator/assistant provide the patient with a high degree of safety and that, contrary to expectation, such operations during surgical residency show the lowest complication rates.

Interestingly, complication rates increase when the 'beginner' shifts from group 3 to group 2, with a peak of 7·8 per cent between 45 and 65 operations (*Fig. 2*). Despite reassuringly low rates of permanent nerve damage (0·5 per cent) the increasing number of temporary lesions is troublesome and may threaten patients in professions which depend on speech. No objective reasons for an increase in difficulty of the operations within group 2 could be identified. Reoperations were excluded from the study and there was no significant difference in age, sex or pathology of the goitres in the three groups. Therefore one may speculate that increasing self confidence may lead to more straightforward and less conscientious preparation, which could explain in part the temporary increase in early functional disturbances. The dramatic decrease in the rates of early functional disturbance in group 1 during the course of the following operations demonstrates the expected learning curve.

It is concluded that complication rates are affected considerably by the extent of surgical experience in a non-linear and complex logarithmic manner. Therefore, in quality assurance analyses, complication rate data should only be compared with respect to the stage of training of the surgeon. Further measures are required to minimize the temporary increase in the complication rates during surgical maturation.

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Accuracy of intraoperative frozen-section analysis of axillary nodes

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Background: Intraoperative assessment of axillary lymph node involvement would allow selection of patients who would benefit from axillary lymph node dissection.
Methods: Eighty-eight patients undergoing mastectomy or wide excision had four nodes sampled and sent for frozen-section examination.
Results: Frozen-section analysis of the nodes was correct in 81 of the 88 patients but missed seven of the 26 patients who had involved nodes on paraffin section (sensitivity 73 per cent).
Conclusion: Frozen-section analysis of axillary lymph nodes as currently practised cannot be recommended for routine use although it may have a role in specific groups of patients.

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Introduction

Involvement of axillary lymph nodes occurs in up to one-half of symptomatic breast cancers and in 10–20 per cent of screen-detected cancers[1]. The presence or absence of lymph node metastases is the most important single prognostic factor and decisions about adjuvant therapy are based on it[1]. Preoperative clinical or radiological assessment of lymph node involvement is inaccurate; only 70 per cent of involved nodes are clinically detectable. Only histopathological assessment of excised lymph nodes provides accurate prognostic information[1]. Axillary surgery has two roles: first, to stage the axilla and, second, as treatment if the axillary nodes are involved. The only patients who benefit from complete axillary dissection are those with involved nodes. Identification of patients without axillary node involvement has been the stimulus behind the development of the sentinel node biopsy[2,3]. One problem with this technique is that the node needs to be removed and submitted for histological assessment before a decision can be taken whether or not to proceed to a full axillary dissection. The one study that has examined frozen-section analysis of sentinel lymph nodes has demonstrated that this technique is associated with a significant false-negative rate[3].

Sampling four axillary nodes is an accurate method of determining whether the axillary nodes are involved[4] although some have failed to identify four separate nodes consistently[5]. Data from Edinburgh suggest that dissecting out four nodes can provide adequate qualitative information on axillary lymph node status[4,6]. Removing more than a single node may increase the accuracy of intraoperative frozen-section analysis over that achieved by frozen section of a single sentinel node.

The aim of this study was to assess the accuracy of intraoperative frozen-section analysis of axillary lymph node samples.

Patients and methods

Eighty-eight patients having either mastectomy or wide local excision for breast cancer had four axillary lymph nodes submitted for frozen-section analysis during the interval 1994–1997. There were specific indications for the use of frozen-section analysis during this time. It was performed either when a patient was considered to be at low risk of axillary lymph node involvement or in an effort to avoid either a full axillary clearance or axillary radiotherapy. The indications for use of frozen-section analysis and the number of patients fulfilling each indication were:

1. Bilateral breast cancer in elderly patients ($n = 8$). The aim was to avoid bilateral axillary clearance or bilateral axillary radiotherapy. One axilla from each patient had nodes removed and submitted for frozen section.
2. Patients undergoing mastectomy for recurrence who had previously been treated by axillary radiotherapy ($n = 19$). All but one of these patients had been treated

for locally advanced breast cancer by breast and axillary radiotherapy following an initial period of primary systemic treatment. In these patients a full axillary dissection would produce a significant risk of lymphoedema.

3 Patients with widespread microcalcification thought likely to be ductal carcinoma *in situ* (DCIS) but requiring mastectomy ($n = 34$). Histological assessment of patients with widespread microcalcification frequently demonstrates invasive foci.
4 Patients with a small invasive breast cancer requiring mastectomy because of widespread DCIS visualized on mammography or diagnosed on biopsy who had not undergone a previous axillary procedure ($n = 26$).
5 Patients who were not suitable for postoperative radiotherapy and in whom there were reasons for avoiding axillary clearance, such as patients with a frozen shoulder or severe rheumatoid arthritis ($n = 1$).

Four or more nodes were removed in a standard axillary node sampling procedure[4] and were sent fresh to the Department of Pathology. Lymph nodes were removed having completed the dissection of the upper mastectomy flap or before the wide local excision. The result of the frozen-section analysis was then available by the time the excisional surgery had been completed. Nodes were bisected and frozen, and sections were cut at approximately 6 µm from the central part of the node and stained with haematoxylin and eosin in the usual way. Sections were examined microscopically and an immediate report was given to the surgeon.

The frozen-section block and any remaining tissue from the specimen was then processed for the preparation of a paraffin block from which 4-µm sections were cut, stained with haematoxylin and eosin and examined by the pathologist. On average three sections from different parts of the node were examined.

The final report always stated whether tumour identified in the paraffin sections was present or not in the original frozen sections so that the surgeon was made aware whether a negative report was a false negative or a missed diagnosis.

There were 408 potential nodes submitted by the surgeon for assessment by frozen section, a mean of 4·6 nodes per patient (median 4). A total of 361 nodes was subjected to frozen-section analysis (maximum of four per patient, as per schedule). As soon as the pathologist identified an involved node, no further nodes were examined. Subsequent paraffin-section assessment demonstrated that a total of 392 of the 408 potential nodes submitted were actually nodes.

If axillary nodes were reported as involved at frozen-section examination, a full level I, II and III axillary clearance was performed. Patients with negative nodes had no further axillary procedure performed at that time. A final paraffin-section report of the nodes submitted for frozen-section analysis was available within 72 h. Patients who were node negative on frozen-section examination but had involved nodes on paraffin-section histology were treated with axillary radiotherapy unless they had previously had this treatment, in which case they had a second operation to remove all the remaining nodes at levels I, II and III.

Results

Of the 361 axillary nodes subjected to frozen-section examination, 330 were reported as negative and 31 were reported as involved. The final paraffin-section histology demonstrated 355 negative axillary nodes and 37 involved nodes.

The results for the 88 patients whose nodes were submitted for frozen section are summarized in *Table 1*. In 69 patients the nodes submitted for paraffin section were negative, but on subsequent histological assessment, seven of these patients were found to have involved nodes. Nineteen patients had involved nodes on frozen section and all were confirmed to have involved nodes on paraffin-section histology. The sensitivity for the detection of involved nodes was 73 per cent (19 of 26), the specificity

Table 1 Results of frozen-section analysis in the five groups of patients

		No of positive tests		
	No of patients	Frozen section	Paraffin section	False negative on frozen section
Bilateral cancer	8	0	0	0
Previous axillary radiotherapy	19	11	13	2
Widespread microcalcification	34	3	3	0
Small cancer	26	5	10	5
Frozen shoulder	1	0	0	0
Total	88	19	26	7

was 100 per cent (62/62), the positive predictive value was 100 per cent (19 of 19) and the negative predictive value was 90 per cent (62 of 69). All false negatives on frozen-section analysis were true false negatives in that none of the metastases were evident even on the paraffin sections of the portion of tissue examined at frozen section. All the subsequent metastases were micrometastases and consisted either of subcapsular deposits or groups of cells in afferent or efferent lymphatics. There were seven false-negative reports. The highest proportion of patients with involved nodes was found in the group who had had previous axillary radiotherapy; the final paraffin-section histology demonstrated metastases in 13 of 19 of these patients. The greatest problem with false-negative frozen-section reports was in the group of women with small cancers. Five of ten of the patients who had involved nodes on paraffin-section histology had microscopic metastases that were not evident on frozen sections. Frozen-section analysis proved accurate in the assessment of patients with widespread microcalcification. This was the group with the lowest incidence of axillary node involvement. In two of the three patients with node metastasis and widespread microcalcification, the pathology showed widespread non-invasive cancer with no evident invasion.

Between three and seven nodes were submitted for frozen-section analysis from the seven patients who had a false-negative analysis. Five of the seven patients on subsequent histology had one node involved but two had two positive nodes. Three of these patients were treated by an axillary clearance performed as a second procedure. In two no further involved axillary nodes were identified by the pathologist in the full clearance specimen. In the other patient there was only a single involved node left in the axilla. The remaining four patients received axillary radiotherapy.

Discussion

Patients likely to be axillary lymph node negative should be undergoing a procedure to assess axillary lymph node status which is associated with minimal morbidity. This includes either a four-node axillary sample[4,6] or a sentinel node biopsy[2,3]. Frozen-section examination of a four-node sample or a single sentinel node offers the opportunity to proceed to axillary clearance in the same operation if any of the nodes examined contain metastatic cancer.

Studies published to date of frozen section of sentinel nodes have shown a significant false-negative rate[3]. It was hoped that by increasing the number of nodes sampled, the accuracy of this technique would improve. The present study has confirmed that routine frozen-section examination of axillary nodes is not sufficiently sensitive, although it is specific. Because of the large number of patients in the present series with negative nodes, the predictive value of a negative frozen section was reasonably high at 90 per cent. This means that over 90 per cent of patients avoided more extensive axillary surgery.

In patients in the present study there were specific reasons for trying to avoid radiotherapy and this makes it difficult to compare results with those published from other centres. This series of patients did not include any with obvious involved lymph nodes or patients with larger tumours. This explains why overall only 26 (30 per cent) of 88 patients had involved nodes. The problem with the present method was that seven patients in this study had involved nodes on paraffin-section histology that were not evident on frozen sections. These women needed to undergo further axillary surgery or radiotherapy. There were psychological implications for patients who were told that their nodes were clear on frozen section, but were informed 2 days later that paraffin-section assessment had demonstrated nodal involvement. The false negatives on frozen section occurred because of the limited sampling which standard frozen-section analysis provides. Newer techniques are currently being developed that use multiple sections across nodes and monoclonal antibodies to detect epithelial cells[7].

Half of the metastases in patients with small cancers were missed at frozen-section examination because the metastases were microscopic and in a subscapular position. Frozen-section analysis was reasonably accurate in women who had had previous axillary radiotherapy, and detected 11 of the 13 patients found to have node involvement on paraffin-section histology. Frozen-section examination did avoid the need for a full axillary dissection in six patients and so avoided the very high rate of lymphoedema associated with combined axillary surgery and radiotherapy. Frozen-section analysis also proved accurate in the group of patients with widespread microcalcification. The greater the extent of microcalcification in the breast the more likely there is to be a focus of invasion which would necessitate an axillary staging procedure. Patients with apparent DCIS on mammography occasionally have involved axillary lymph nodes[8]; three of 34 patients had positive axillary nodes in this study. Of interest, two of the three patients with involved axillary nodes had no apparent invasion on histological assessment; had they not undergone axillary node sampling, the presence of invasive disease would have gone undetected.

The use of frozen sections to assess the status of axillary lymph nodes may have a role in specific groups of patients.

Until newer techniques are fully developed, routine frozen-section assessment of axillary nodes cannot be recommended.

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Original article

Factors leading to local recurrence or death after surgical resection of phyllodes tumours of the breast

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Background: Local recurrence and death from metastases are occasional, but consistent, themes in reports of patients with phyllodes tumours. Factors that might contribute to these outcomes were sought.

Methods: Data from 38 patients with a phyllodes breast tumour were reviewed retrospectively, reclassifying the pathological material using the Pietruszka and Barnes criteria.

Results: At a median of 12 months, nine patients had developed a local recurrence and four had died from metastases. Following local excision in 24 patients (for diagnosis in 13, for 'fibroadenoma' in nine and for phyllodes tumour in two patients), 13 had no further surgery and five had local recurrence (three of eight benign tumours, two of two malignant tumours). Wide local excision or mastectomy in 18 patients was followed by four recurrences (one of eight borderline tumours, three of ten malignant tumours). All patients with recurrence had margin involvement on histological examination, but not all patients with margin involvement developed recurrence. Lack of statistical correlation between local recurrence and age, delay, size, grade or type of surgery was confounded by selection bias for more extensive surgery for malignant tumours. Death correlated with size ($P = 0{\cdot}05$) and grade ($P = 0{\cdot}03$) of tumour.

Conclusion: Inadequate preoperative diagnosis ('fibroadenoma' or failure of triple assessment) frequently led to local excision with positive margins. Without revision this often resulted in local recurrence. Local recurrence of any grade was usually followed by further recurrence. Death was related to tumour size and histological grade, confirming these as prognostic factors.

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Introduction

Phyllodes tumour of the breast is uncommon and characterized by a local recurrence rate of approximately 20 per cent after surgical resection and a 5-year survival rate of 90 per cent[1–23]. This variable behaviour must partly be a function of the inherent qualities of the tumour, which has resulted in several histological classification systems: Treves and Sunderland (benign and malignant)[24], Pietruszka and Barnes (benign, borderline and malignant)[6], similar categories by Azzopardi, but using different criteria[25], and that of the World Health Organization (low, intermediate and high grades)[26]. The outcome could also be modified by clinical factors such as patient age, delay in diagnosis or misdiagnosis, and inappropriate and inadequate management. Factors that could have predisposed to local recurrence or death were analysed retrospectively in a series of patients with phyllodes breast tumour.

Patients and methods

The clinical features of 38 patients with a phyllodes tumour, who were managed between 1975 and 1996 at the Groote Schuur Hospital Breast Clinic, a primary and tertiary referral centre, were reviewed and collated. All were women, with a median age of 44 (range 17–65) years. Twenty-two tumours occurred in the right and 16 in the left breast. The median size was 8 (range 2–30) cm. All pathological material was reviewed, and the tumours were recategorized according to the criteria of Pietruszka and Barnes[6], a system that defines three groups of tumours primarily according to the most active region of the neoplasm. Thus, 'benign' tumours had four or fewer mitoses per ten high-power fields (HPFs), 'borderline' tumours had between five and nine mitoses per ten HPFs, and 'malignant' tumours had ten or more mitoses per ten HPFs. Specimens with tumours within 1 mm of the excision margin were regarded as having involved margins. The surgical procedure was categorized into three types: local excision, wide local excision or quadrantectomy, and simple mastectomy. One patient was lost to follow-up at 56 weeks.

Local recurrence and death were correlated with patient characteristics, histological features and the type of primary surgical intervention, using the χ^2 test with Fisher's exact probability test.

Results

Preoperative diagnosis

The preoperative diagnosis (based on clinical features combined with one or more diagnostic tests) was inconclusive in 13 patients, who underwent diagnostic local excision. Of the individual tests, mammography was incorrect or inconclusive in 15 of 23 tumours, cytology in 16 of 24 and core biopsy in 12 of 27. No patient underwent ultrasonography. In a further nine patients the tumour was diagnosed clinically as a fibroadenoma, and excised without any initial investigation A further two patients had local excision of correctly diagnosed lesions. Thus a total of 24 patients underwent initial local excision of a phyllodes tumour. After histological confirmation of the diagnosis and the finding of margin involvement in the majority, 11 patients had a more extensive excision. The remaining 13 patients were either not offered further treatment (two of the benign variants) or refused it (any variant).

Local recurrence

Nine patients developed local recurrence after a median of 12 (4–84) months (*Table 1*). All had tumours with histological margin involvement. The presence of margin involvement did not, however, make recurrence inevitable, although it was almost invariable with malignant tumours. While local recurrence occurred with each histological grade of tumour and after each type of primary surgery, benign lesions recurred only after primary local excision and not after wide local excision or mastectomy (which was necessitated by large tumour size in three patients). Malignant tumours recurred after each type of surgical procedure, but least often following mastectomy. None of the variables of age, delay, side, size, histological grade or type of primary operation showed a significant correlation with local recurrence.

The event of local recurrence appeared to predispose to further recurrence: six of the nine patients with recurrence developed further recurrence at a median of 58 (10–146) months, and a further three had a third recurrence at a median follow-up of 143 months. This propensity to recurrence occurred with both benign and malignant variants, and after both local excision and mastectomy. Second and third recurrences developed irrespective of the histological grade of the primary tumour or the type of surgical intervention.

Metastatic disease and death

Four patients with malignant tumours developed generalized haematogenous metastases and died after a median of 17 (12–145) months; three of these patients had suffered frequent local recurrences. There was a correlation between death and the size ($P = 0{\cdot}05$) and histological grade ($P = 0{\cdot}03$) of the tumour, but not with age, delay, type of surgery or local recurrence.

Discussion

The median rate of local recurrence reported after surgery for phyllodes tumours is 20 per cent[2,6,7,9–11,14,15,17,20], a proportion similar to that found in this study. A significant contributing factor was inaccurate diagnosis ('fibroadenoma') in the young and inconclusive diagnosis with triple assessment, or even core biopsy, in older patients. Local excision was thus frequently required for diagnosis, in contrast to patients with breast cancer investigated over the same interval, when an accurate diagnosis was made by triple assessment in approximately two-thirds of cases.

Table 1 Local recurrence rates according to tumour type and treatment

Grade	Local excision	Wide local excision	Mastectomy	Total
Benign	3 (3) of 8 (6)	0 (0) of 4 (1)	0 (0) of 3 (1)	3 (3) of 15 (8)
Borderline	0 (0) of 3 (1)	1 (1) of 2 (1)	0 (0) of 6 (3)	1 (1) of 11 (5)
Malignant	2 (2) of 2 (2)	1 (1) of 2 (1)	2 (2) of 8 (3*)	5 (5) of 12 (6*)
Total	5 (5) of 13 (9)	2 (2) of 8 (3)	2 (2) of 17 (7)	9 (9) of 38 (19)

Values in parentheses indicate resection margin involvement. *A 38-year-old patient underwent mastectomy for a malignant phyllodes tumour, had disease 1 mm from the resection line, and had not suffered recurrence when lost to follow-up at 56 weeks

The remainder were made with core biopsy[27]. Triple assessment is insensitive and not specific in the diagnosis of phyllodes tumour. Core biopsy may be suggestive, but the pathologist may be reluctant to make a definitive diagnosis with amount of material yielded.

While local excision was frequently necessary and appropriate for diagnosis, it was inadequate as a treatment. Local recurrence often developed after local excision of benign lesions, and was invariable with malignant ones. This was in striking contrast to the low recurrence rates after initial or subsequent radical surgery. The problem was to persuade patients to undergo additional radical surgery after local excision, even those with marginal involvement or malignant variants. Many declined to have this. In many previous reports there is similar frequent reference to 'positive or inadequate surgical margins'[12,16,17,21,23], probably indicating that additional surgery was not undertaken after incomplete excision. All patients with local recurrence had histological marginal involvement, confirming this as a strong risk factor.

Other factors implicated in the development of local recurrence with or without subsequent metastatic death include the type of surgery and surgical margins[16,17,21,23], tumour size[15,17], stromal overgrowth[1,5,11,15], cellular atypia, tumour necrosis[10] and mitotic activity[2,19,26]. Other authors have suggested combinations of individual parameters to explain recurrence[6,13,21]. Clearly, an unfavourable outcome must be the result of many interreacting variables. On statistical analysis it appeared in the present series that local recurrence was not related to age, delay in diagnosis, side, size, grade or type of surgery. These results may have been confounded by selection bias for type of surgery (the more malignant, the more likely was radical surgery). The major variables of grade and type of surgery may have been obscured. Resection margin involvement was confirmed as a strong, but not absolute, prognostic factor for recurrence.

A further observation was that the event of local recurrence made further local recurrence likely, with each grade of lesion. This could be easy to understand with borderline and malignant lesions, but it lacks explanation with benign phyllodes tumours. Unpredicted by histological features, some benign lesions appear to have a propensity to local recurrence.

Size and grade of phyllodes tumour were significantly related to metastatic death, a relationship that has been reported frequently[3,6,10,16,19,22]. Here, the biological nature of the lesion and the probable pre-existence of metastases probably outweighed selection bias for type of surgery.

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Experimental study of the effect of intraperitoneal heparin on tumour implantation following laparoscopy

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Background: Conclusions drawn from clinical reports of port site metastases following laparoscopic resection of intra-abdominal malignancy are now supported by a burgeoning experimental literature which suggests that laparoscopy promotes tumour metastasis to wounds. This study investigated the effect of intraperitoneal blood and heparin on the incidence of tumour cell implantation and port site metastasis.

Methods: Twenty-four Dark Agouti rats underwent laparoscopy with carbon dioxide insufflation and the instillation of a tumour cell suspension and/or blood into the peritoneal cavity. Rats were allocated randomly to one of the following study groups (six rats per group): (1) controls; (2) intraperitoneal blood (2 ml blood introduced from a syngeneic donor rat); (3) intraperitoneal heparin; (4) intraperitoneal blood and heparin. Rats were killed 7 days after the procedure, and the peritoneal cavity and port sites were examined for the presence of tumour.

Results: Tumour implantation and port site metastases were reduced by the intraperitoneal administration of heparin, but increased by the presence of intraperitoneal blood.

Conclusion: The results of this study suggest that tumour implantation following laparoscopy is promoted by the presence of intraperitoneal blood and that this effect may be reduced by the use of intraperitoneal heparin.

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Introduction

The use of laparoscopic techniques for the resection and staging of intra-abdominal malignancy offers several possible advantages over standard open surgical techniques, including shortened hospital stay, more rapid return to work and decreased pain. However, acceptance of these techniques has been limited by concern about the possible facilitation of tumour spread to port sites[1–3].

Experimental studies suggest that laparoscopy facilitates tumour implantation and the development of port site metastasis[3–8]. While the mechanism of this phenomenon is not yet clear, not all cases are easily explained by direct contamination or seeding of port sites from contaminated instruments[3,9,10]. Specific properties of a pneumoperitoneum, such as the nature of the insufflation gas and possible aerosolization of tumour cells, may play an important role[5,11–13].

The use of intraperitoneal heparin to reduce tumour cell adhesion and consequent implantation has been proposed as a preventive strategy for port site metastases[14,15]. Goldstein *et al.*[15] reported an increased tumour burden in mice when the peritoneum was disrupted before introducing tumour cells into the abdomen. This effect was reduced in mice receiving prophylactic intraperitoneal irrigation with heparin. Jacobi *et al.*[14] also reported a beneficial effect on intraperitoneal tumour cell growth following heparin administration in a rat laparoscopy model which used a colonic adenocarcinoma cell suspension.

To evaluate further the preventive possibilities of heparin, this study investigated the influence of intraperitoneal blood on the generation of laparoscopy-associated metastases and the ability of heparin to prevent them, using an established experimental model.

Materials and methods

The effect of heparin on tumour growth following laparoscopic surgery was evaluated using a laparoscopic model which has been described in detail previously[6]. This involved the introduction of a suspension of mammary adenocarcinoma tumour cells into the peritoneal cavity of an immune-competent, syngeneic rat strain.

Twenty-four Dark Agouti (DA) rats underwent laparoscopic insufflation and intraperitoneal instillation of a suspension of 2 × 10^7 tumour cells. They were then randomized to one of the following study groups (six rats per group): group 1 (control) – no additional substances introduced into the peritoneal cavity; group 2 (blood) – intraperitoneal injection with 2 ml fresh blood; group 3 (heparin) – intraperitoneal injection with 200 units heparin; group 4 (blood and heparin) – intraperitoneal injection with 2 ml fresh blood and 200 units heparin.

All rats were anaesthetized throughout the surgical procedures and the respiratory status of the animals was monitored throughout. Surgical procedures were performed under sterile operating conditions. Pneumoperitoneum was achieved using a conventional Veress needle placed through a right hypochondrial stab wound (*Fig. 1*). A disposable minilaparoscopy cannula (US Surgical, Norwalk, Connecticut, USA) was used to provide access for a 2-mm minilaparoscope (Imagyn, Laguna Niguel, California, USA) with attached conventional laparoscopy camera. Two additional 'ports' were inserted: an 18-G cannula in the left hypochondrium, which was left open throughout the procedure to vent the insufflation gas, and a 16-G cannula in the left lower quadrant, for the introduction of tumour cells, heparin and blood. After commencing gas insufflation and placing all 'ports', a 200-μl volume of tumour cell suspension (containing 2 × 10^7 tumour cells), prepared using a previously described technique[4], was introduced into the peritoneal cavity.

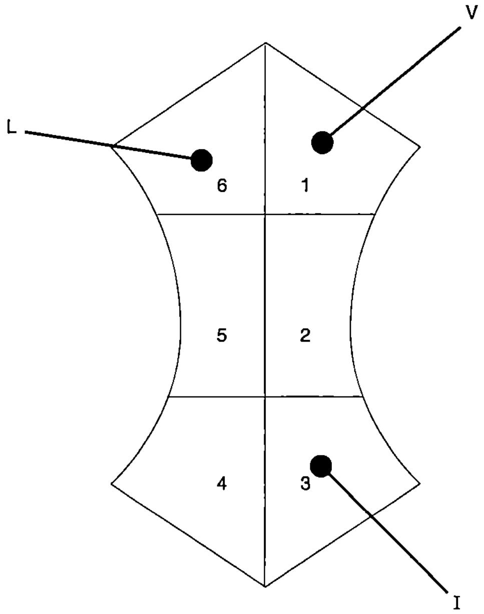

Fig. 1 Division of the abdominal cavity into six sectors and location of trocar entry sites. I, cannula for introduction of tumour, blood and heparin; V, venting cannula; L, laparoscope cannula

The blood introduced into the peritoneal cavity of the rats in groups 2 and 4 was collected from a donor DA rat by cardiac puncture under general anaesthesia. This was administered into the peritoneal cavity 2 min after the tumour cell suspension. Heparin (heparin sodium, porcine mucous; David Bull Laboratories, Mulgrave, Victoria, Australia) was administered intraperitoneally to rats in groups 3 and 4, 4 min after the tumour cell suspension (and 2 min after the blood in group 4). Gas was insufflated at a rate of 0·4 l/min and a pressure of 2 mmHg for a further 40 min, with a constant gas flow maintained through the venting cannula. The 'ports' were then removed and the puncture sites closed with sutures.

Some 7 days later the rats were killed and their abdominal cavities examined for the presence of tumour. The abdomen was divided into six sectors as illustrated in *Fig. 1* to facilitate scoring of tumour implantation and growth. Peritoneal tumour deposits in each sector were scored for tumour density using the peritoneal cancer density index proposed by Eggermont *et al.*[16]: 0, no intraperitoneal tumour; I, less than three minute tumour foci; II, moderate tumour; III, abundant or confluent tumour. Representative samples were also obtained for histological confirmation of the macroscopic assessment. The port sites were examined specifically for macroscopic evidence of tumour implantation.

The protocol for this study was approved by the animal ethics committees of the Institute of Medical and Veterinary Science and the University of Adelaide, Adelaide.

Results

Before operation the rats in each group were of a similar weight, and all animals gained a similar amount of weight after operation. *Tables 1* and *2* provide a summary of tumour implantation. One rat in each of the heparin and the blood plus heparin groups was totally free of tumour. All rats in the blood-instilled group had tumour in all sectors compared with three rats in both the control and the heparin plus blood groups. In the heparin-instilled group no rats had tumour in all sectors.

In the blood-only instillation group tumour implantation was enhanced compared with that in controls (*Table 1*). A decrease in tumour implantation was observed in the heparin and the blood plus heparin groups com-

Table 1 Peritoneal tumour index: number of sectors involved with each tumour grade

Grade	Control	Blood	Heparin	Blood and heparin
0	4	0	27	10
I	5	8	6	8
II	15	16	3	8
III	12	12	0	10

Table 2 Number of port sites with tumour present (18 wounds per group)

Group	No. of sites
Control	17
Blood	18
Heparin	5
Blood and heparin	10

pared with controls. In the heparin group 27 of the 36 sectors had no visible tumour growth. This compared with ten, four and none of the 36 sectors in the blood plus heparin, control and blood-alone groups respectively. When a 2 × 2 contingency table was constructed to compare heparin (groups 3 and 4) with no heparin (groups 1 and 2), a significant reduction in the incidence of tumour implantation in the sectors was evident: 37 (51 per cent) of 72 sectors were free of tumour following heparin *versus* four (6 per cent) of 72 without heparin ($P < 0{\cdot}0001$, Fisher's exact test). When the influence of intraperitoneal blood was evaluated in a similar fashion, i.e. blood (groups 2 and 4) *versus* no blood (groups 1 and 3), blood was associated with tumour growth in significantly more sectors: 62 (86 per cent) of 72 sectors *versus* 41 (57 per cent) of 72 ($P = 0{\cdot}0002$, Fisher's exact test).

All port sites in the blood-alone group and all but one in the control group were involved with tumour (*Table 2*). This compared with a reduced incidence of port site involvement in the two heparin groups (15 *versus* 35; $P < 0{\cdot}0001$, Fisher's exact test). The group administered heparin alone was least likely to develop port site metastases. Analysis of the influence of blood (groups 2 and 4) *versus* no blood (groups 1 and 3) on the incidence of port site metastases, however, did not demonstrate a significant increase in incidence following the administration of intraperitoneal blood (28 *versus* 22; $P = 0{\cdot}20$, Fisher's exact test).

Discussion

Since Dobrönte *et al.*[17] first reported the phenomenon of port site metastasis in 1978, it has become clear that the laparoscopic manipulation of both abdominal and thoracic malignancies can be followed by metastasis to surgical access wounds[18–20]. Experimental work using small animal models[4,6,7,21,22] suggests that the incidence of wound metastasis is increased following laparoscopic surgery compared with conventional open surgery. Nevertheless, until the outcomes from large clinical randomized trials of laparoscopic *versus* open surgery for cancer become available, this issue will remain open to controversy[3].

A variety of explanations for the phenomenon of laparoscopic port site metastasis has been advanced, and more recently preventive strategies have been advocated. One such strategy is the use of substances that might influence tumour adhesion and thereby prevent implantation and growth. Goldstein *et al.*[15] recently reported a reduction in tumour implantation following intraperitoneal heparin administration in a sham laparoscopy model which utilized a murine bladder tumour cell suspension. They also demonstrated that this effect was not due to a direct toxicity effect of heparin on the tumour cells *in vivo*. Jacobi *et al.*[14] also described reduced intraperitoneal tumour growth in a rat laparoscopy model following intraperitoneal administration of heparin. Heparin is a naturally occurring anticoagulant derived from bovine or porcine mucosa. It binds to fibronectin, decreases tumour cell adherence by competitive inhibition[15] and might inhibit tumour growth by blocking tumour cell attachment to areas of peritoneal injury[14]. Alternatively, heparin may inhibit tumour cell attachment by restoring the normally negative surface charge of peritoneum, which is altered by injury[23].

In the present study, the use of intraperitoneal heparin was associated with a significant reduction in both general tumour implantation within the peritoneal cavity and port site metastases. The presence of intraperitoneal blood, on the other hand, resulted in an increased likelihood of tumour implantation (although not of port site metastases). Results from preliminary cell culture studies in the authors' laboratory (unpublished data) suggest that this is not likely to be a direct cytotoxic effect of heparin on the tumour cell line used for these studies, as heparin actually promoted tumour cell growth in *in vitro* studies. Despite this, the effect of heparin in the present study was advantageous *in vivo*. One possible explanation for this discrepancy is that tumour cell adherence and implantation is facilitated by components of blood, possibly the fibrin matrix, and that this can be reversed in part by the use of heparin. Supporting this hypothesis is the adverse effect of blood in the peritoneal cavity, which promoted tumour implantation and growth in the present study. It is important to realize that, even though the blood used in this study was from another rat, the DA strain is inbred, with all DA rats effectively genetically identical to one another. This enabled the influence of a controlled amount of blood on tumour growth to be determined.

As bleeding during surgery can be prevented in part, but never completely, by meticulous surgical technique, the adverse effect of blood demonstrated in this study is unlikely to be eliminated reliably by even the most meticulous laparoscopic surgeon. It is possible that tumour cells trapped in a blood clot might be afforded protection from scavenger mechanisms, and that this might be partly reversed or prevented by heparin. Alternatively the reduction in port site metastasis could be due to a heparin-induced decrease in tumour cell adherence to the laparoscopic cannulas.

A possible criticism of this study is the small number of animals used in each study group. Nevertheless, the results clearly support the conclusions drawn, with inspection of the results in the tables highlighting the advantage of heparin and the negative effect of intraperitoneal blood. Statistical analysis has confirmed the conclusions drawn.

The authors believe that this study is important within the context of laparoscopic surgery for cancer. It confirms that intraperitoneal administration of heparin is a strategy that should be considered for further clinical investigation, and that the presence of intraperitoneal blood might promote tumour growth in the laparoscopic environment. Further investigation of these findings is warranted.

Acknowledgements

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Original article

Mechanism of action of antireflux procedures

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Background: To define the clinical role of antireflux surgical procedures a proper understanding of their mode of action is required. The aim of this study was to investigate the impact of total or posterior partial fundoplication on the function of the lower oesophageal sphincter (LOS) in the basal state as well as during stimulation.

Methods: Patients with chronic reflux ($n = 24$) were randomized either to a total fundic wrap or to a posterior partial (Toupet) fundoplication. Basal LOS function was investigated as well as the response to inhibitory stimuli 4 years after operation. Inhibitory stimulation was elicited by water swallows and by gas distension (750 ml air insufflation into the stomach).

Results: Basal LOS tone was substantially higher ($P = 0\ 01$) after a total than a partial wrap, as was the nadir pressure after water swallows (10 1 *versus* 3 4 mmHg). Body position did not affect this difference. Transient LOS relaxations occurred only occasionally in the basal state. The frequency of transient LOS relaxation increased somewhat during the first 10 min of stomach distension with more occurring in patients who underwent a Toupet procedure. Common oesophagogastric cavities were more often seen in this latter group of patients after gas distension of the stomach.

Conclusion: These physiological observations on the LOS after total and posterior partial fundoplication explain the observed clinical differences in favour of the latter operation. The partial fundoplication seems to restore the physiology of the gastro-oesophageal junction more adequately, allowing air to be vented from the stomach without jeopardizing the antireflux barrier.

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Introduction

Fundoplication procedures are popular in the long-term management of chronic gastro-oesophageal reflux disease (GORD) and their efficacy has been well established[1–3]. Side-effects occur after such operations and after a total fundic wrap dysphagia, inability to belch and vomit, postprandial fullness, bloating and pain, and sometimes socially embarrassing flatus are described in varying frequencies[4–8]. Technical factors have been suggested to explain some of these problems but until recently no firm conclusions could be drawn from available reports[5,8,9]. A potential key factor behind these symptoms may be incomplete venting of air from the stomach. Transient lower oesophageal sphincter (LOS) relaxations are known not only to be of particular pathogenetic importance in GORD but also to play a pivotal role in adequate venting of air from the stomach[10–12]. It has been shown recently that a total fundic wrap durably controls reflux, as does a partial posterior fundoplication (Toupet)[13]. In the long-term follow-up after these operations, it was noted that patients who had a total fundic wrap more frequently complained of socially embarrassing flatus, which might originally be caused by an impairment in the ability to vent air from the stomach. Hypothetically, these operations might therefore exert different effects on important reflux-preventing mechanisms such as LOS tone, ability of the LOS to relax to proper stimuli and on the frequency of transient LOS relaxations[14,15]. Within the framework of a randomized clinical trial of total *versus* Toupet fundoplication these LOS mechanisms have been studied in the basal state as well as after gas distension of the stomach.

Patients and methods

Twenty-four patients, originally enrolled into a randomized controlled clinical trial[13] comparing a total fundic wrap (complete mobilization of the fundus by dividing all short gastric vessels) and partial posterior fundoplication (Toupet, 180–200°), agreed to undergo a complete study programme at the time of long-term follow-up after the original operation. The study protocol was approved by the local ethics committee and informed consent to participate in the study was obtained from each patient.

The relevant investigations were carried out at a mean of 54·5 (range 35–85) months after the operation, the technical details of which have been described elsewhere[13]. Thirteen patients had originally been randomized to total fundoplication (11 men; mean age 49·8 (range 35–61) years) and 11 to partial fundoplication (seven men; mean age 47·9 (range 25–68) years). All patients had complete control of their reflux disease as assessed by the level of symptom control, and by use of endoscopy and ambulatory 24-h pH monitoring (*Table 1*).

Manometry was performed by use of a water-perfused multiple-lumen pressure catheter with side holes positioned at 5-cm intervals. The catheter was introduced into the oesophagus through one nostril. The manometric assembly contained polyethylene tubes bound together with corresponding lateral openings. On the distal end of the catheter was a sleeve sensor[17] which was positioned to straddle the gastro-oesophageal junction. In the side hole distal to the sleeve the intragastric pressure was measured continuously. Each portion of the catheter assembly was connected to a pressure transducer and constantly perfused with water (0·5 ml/min) via a low-compliance capillary system (Andorfer system; Andorfer Medical Specialities, Greendale, Wisconsin, USA).

The patients were investigated after an overnight fast and, during the investigation, kept recumbent in the right lateral position for 30 min and thereafter in the sitting position, whereupon another 10 min were allowed for stabilization; gas (750 ml air) was then insufflated into the stomach.

The recording system was calibrated to atmospheric pressure and to standardized hydrostatic pressures before and after each examination. At the time of each assessment, the reference pressures were the intraluminal end-expiratory oesophageal pressure for oesophageal body motor events and the end-expiratory intragastric pressure for LOS tone. LOS sphincter tone was recorded at 1-min intervals when a stable pressure level was prevailing at a time when there was no interference from swallows.

Table 1 Clinical assessment, endoscopic findings and 24-h pH monitoring data in patients operated on for chronic gastro-oesophageal reflux disease

	Nissen–Rossetti ($n = 13$)	Toupet ($n = 11$)
Heartburn (no symptoms)	12	10
Acid regurgitation (no symptoms)	13	9
Dysphagia (no symptoms)	12	11
Flatus (no symptoms)	4	6
Endoscopic grade		
0	12†	10
1	0	1
Fraction of time pH < 4 (%)*	0·4(0·2)	3·5(1·7)

*Values are mean(s.e.) (range of normality less than 4·7 per cent). Endoscopic assessment was made according to Sandmark *et al*[16], †data not available for one patient

The manometric recordings in the recumbent and sitting positions were always started by repeating ten water swallows, each elicited by a bolus of 5 ml of water at room temperature. Each water swallow was separated by an interval of at least 15 s.

A complete transient LOS relaxation was defined as an abrupt (more than 1 mmHg per s) fall in the LOS pressure exceeding 5 mmHg to a level of 2 mmHg or less above intragastric pressure, with a duration of at least 5 s[12]. No swallows were allowed during the 5 s preceding the onset of LOS relaxation. Postswallowing transient LOS relaxations were, however, included in the analysis. Recording of LOS tone was continued for 30 min after air insufflation as well. The completeness of a transient LOS relaxation was also assessed in relation to the nadir pressure during repeated water swallows. This is of particular importance after fundoplication which exposes the native LOS to external compression by the fundic cuff[15]. Separate notes were made of transient relaxations in which the nadir pressure reached below 2 mmHg relative to intragastric pressure[15]. The recordings were analysed for the occurrence of gas reflux as indicated by the presence of common oesophagogastric cavities[10]. For the purpose of this study, a common cavity was defined as an abrupt increase in intraoesophageal pressure to intragastric pressure in at least two oesophageal recording sites.

To assess the intra-abdominal length and the total length of the high-pressure zone in the LOS, a station pullthrough technique was used; the probe was withdrawn in 0·5-cm steps and kept at each level for at least 30 s or until the recordings stabilized. The length of the intra-abdominal part of the high-pressure zone was calculated from the pressure profile as the distance from the point of the first stable pressure rise above the fundus pressure to the first point of negative pressure to occur on inspiration.

All manometric recordings were analysed by one investigator (L.R.), without knowledge of the nature of the surgery undergone by each patient.

Statistical analysis

Statistical analyses were carried out with the χ^2 test, Student's t test and non-parametric tests (Mann–Whitney U test, Wilcoxon signed rank test). $P < 0{\cdot}05$ was considered to be significant. Data are expressed as mean(s.e.).

Results

Basal sphincter tone was quite stable in both fundoplication groups (*Fig. 1a*) but was significantly higher in those who underwent total fundoplication both in the sitting and recumbent body positions ($P = 0·01$). Insufflation of air into the stomach had only a marginal effect on LOS sphincter tone. Despite these differences in basal tone, there was no difference in the intra-abdominal length of the LOS (*Fig. 1b*). The nadir pressure of the LOS induced by water swallows was significantly higher in patients with a total fundoplication (10·1(1·7) mmHg) than the value of 3·4(0·5) mmHg in those who had a partial fundoplication ($P = 0·003$). The number of transient LOS relaxations in the recumbent and sitting positions is illustrated in *Fig. 2*, which shows comparatively few events in the basal state and a marginal increase after gas insufflation into the stomach. The few transient LOS relaxations elicited by gastric distension occurred in the first 10 min and there were more in the Toupet group, but otherwise there were no significant differences between the two study groups. The nadir pressure during LOS relaxations was 6·5(2·6) mmHg in those having a total fundic wrap, which was higher than the value of 2·6(0·8) mmHg in those having a Toupet fundoplication (P not significant). Only exceptionally were complete transient LOS relaxations recorded. On recording the number of common cavities during transient LOS relaxations after gas insufflation into the stomach, nine events were noted in seven patients who underwent a partial fundoplication and only one in those with a total fundoplication ($P = 0·005$).

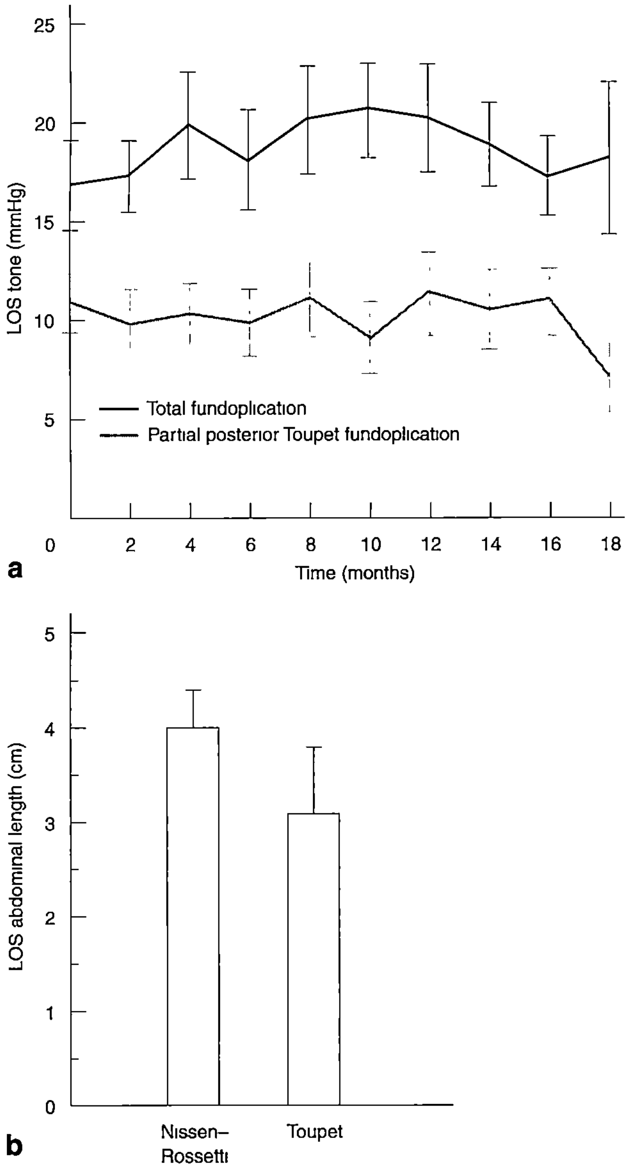

Fig. 1 **a** Mean(s.e.) basal lower oesophageal sphincter (LOS) tone assessed by use of a sleeve sensor and **b** intra-abdominal length of the LOS in patients operated on with either a total fundoplication or a partial posterior Toupet fundoplication

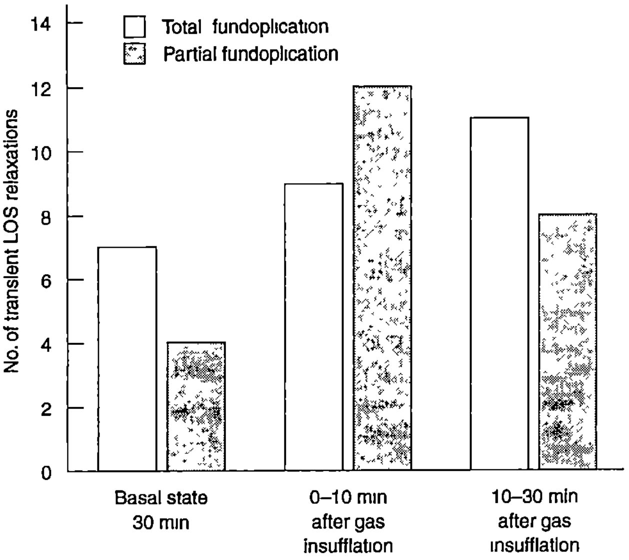

Fig. 2 Transient lower oesophageal sphincter (LOS) relaxations in the basal state (recumbent) and after gas insufflation into the stomach in patients operated on with either a total or partial fundoplication. The total number of transient LOS relaxations for the entire group of patients ($n = 24$) is shown

Discussion

There has been intensive debate over the significance of different factors which might determine the level of success of antireflux surgery. This is an important topic, not least with the objective of better standardizing antireflux surgery and minimizing side-effects. By using different measuring techniques, numerous studies have shown an increase in LOS tone after a variety of fundoplication procedures[14]. This continuous assessment of LOS tone over a longer time period by use of a sleeve sensor revealed that the LOS pressure was substantially higher after total fundoplication than after partial posterior fundoplication. In the latter group the pressure levels recorded in the LOS were very close to what is seen in normal healthy controls[10–12]. In this context it is relevant to recall the previously expressed view that a total fundoplication might overcorrect the mechanical deficiencies in the gastro-oesophageal junction, eliciting a supercompetent cardia[18–20]. In neither group, however, did basal LOS tone ever reach a level at which free reflux is considered to occur. Similar mechanical consequences may also induce obstructive complaints and/or manometric sequelae, which are not always easy to interpret correctly[19,21].

Transient LOS relaxation is a major mechanism of reflux in normal subjects and also in patients with GORD. There are some inconsistencies in the reported frequency of transient LOS relaxations in these patients. One report[21] claimed that 70 per cent of reflux events in patients with GORD were associated with transient LOS relaxations. Other studies have found this to be the case in only about 40 per cent[12,22,23]. The remaining reflux events were caused by combinations of other mechanisms such as swallowing-induced LOS relaxations, absent basal LOS pressure, strain and also unknown causes. Recent studies have shown that a total fundic wrap reduces postprandial reflux by affecting the frequency of transient LOS relaxations[23]. Similar studies have also demonstrated that these operations render swallowing-induced LOS relaxations incomplete[15], presumably by mechanical compression of the LOS segment. These observations are of major clinical significance since they suggest that these operations restore the physiology of the gastro-oesophageal junction. The definition of transient LOS relaxation has, however, to be modified in studies similar to the present one in which not only was significantly higher basal sphincter tone observed in those having a total fundoplication compared with partial fundoplication but also the nadir pressure after water swallow was significantly lower in the latter patients. Again nadir pressure was seldomly at a level which is considered to allow free reflux (less than 2 mmHg). A low frequency of transient LOS relaxations, as defined above, was also recorded in this study, when assessed in the recumbent as well as in the upright body position. Similarly, gas insufflation into the stomach seldomly elicited transient LOS relaxations. Despite the fact that the Toupet fundoplication only encircles half of the oesophageal circumference, it was not possible to demonstrate a difference in the frequency of transient LOS relaxations between the two fundoplication groups both in the basal state and after gas insufflation into the stomach. A frequent observation was, however, that the nadir pressure during transient LOS relaxation was lower in patients who had a partial fundoplication.

An important indication of venting of air from the stomach is the occurrence of a common cavity during manometry[10,24]. This event is represented mechanically by an intragastric pressure superseding the sphincteric pressure during relaxation and transmitted into the lumen of the body of the oesophagus. Significantly fewer common cavities were registered in patients having a total fundoplication. These results provide an explanation for the clinical finding of fewer problems with flatus after partial fundoplication. In this context it should be mentioned that, except for increased flatus, many alleged postfundoplication symptoms are present before operation in patients with chronic GORD[25].

After total fundoplication the relatively high nadir LOS pressure excludes swallow-induced reflux and the absence of complete relaxation of the sphincter in association with transient relaxation explains the mechanism of reflux control. However, fundoplication surgery is more than just wrapping the stomach around the distal oesophagus causing a mechanical buttressing of the area. The operation reduces the hiatal hernia by the dissection and mobilization of the oesophagus and positioning of the crural sutures. This anatomical restoration *per se* might have the potential to prevent reflux by reducing the hiatal hernia, and by improving oesophageal clearance and crural function. Incomplete LOS relaxation after operation might also be induced by neural mechanisms since mobilization of the fundus of the stomach divides connections between gastric mechanoreceptors in that area and the oesophageal sphincter region. There is no doubt that vagal inhibitory fibres innervate the LOS and are responsible for swallowing-induced and even transient LOS relaxations. These fibres enter the oesophagus well above the fundic wrap. On the other hand, animal experiments might be interpreted in favour of a local denervation effect after similar operations[26,27]. The complete division of the short gastric vessels in patients undergoing a total wrap might, however, be followed by more complete denervation. In this context it should be remembered that a similarly low frequency of transient LOS relaxations after gas distension was observed in the two study groups, although the mechanical consequences on the LOS area differ between the two operative procedures, as illustrated by the data on basal LOS tone. One experimental approach which would cast further light on this question would be to study patients randomized to either complete division of all short gastric vessels or leaving them intact at the time of constructing a total fundoplication[28].

In conclusion, the present results offer a physiological explanation for the observed clinical advantage of Toupet partial fundoplication in the form of less troublesome flatus. These patients maintain their ability to vent air from the stomach, which is accomplished without jeopardizing important reflux-preventing mechanisms. The current observations on LOS function after total or partial fundoplication imply that the latter operation has the advantage of restoring the physiology of the gastro-oesophageal junction.

Acknowledgements

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Original article

Inhibition of platelet-activating factor, intercellular adhesion molecule 1 and platelet endothelial cell adhesion molecule 1 reduces experimental pancreatitis-associated gut endothelial barrier dysfunction

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Background: Endothelial barrier dysfunction is a critical link in the development of tissue injury and organ dysfunction, via upregulation and exposure of adhesion molecules, intercellular signals and leucocyte–endothelial cell interactions. Inhibitors of inflammatory mediators and receptors have been suggested as a means of downregulating the cascade of both local and systemic inflammation.

Methods: The potential therapeutic inhibition of platelet-activating factor (PAF), intercellular adhesion molecule (ICAM) 1 and platelet endothelial cell adhesion molecule (PECAM) 1 was investigated in pancreatitis-associated gut endothelial dysfunction in rats, by treatment with a PAF antagonist (lexipafant, BB-882) and monoclonal antibodies against rat ICAM-1 (anti-ICAM1-Mb) and PECAM (anti-PECAM1-Mb). Alterations in gut endothelial barrier dysfunction and leucocyte recruitment, and systemic levels of interleukins were evaluated.

Results: Plasma exudation measured by the albumin leakage index and tissue leucocyte recruitment in the distal small intestine and colon increased significantly 12 h after induction of pancreatitis and treatment with saline. These alterations were to varying degrees counteracted by treatment with lexipafant, anti-ICAM1-Mb or anti-PECAM1-Mb. Alterations in levels of interleukin (IL) 1 paralleled the changes in gut endothelial barrier dysfunction and leucocyte trapping.

Conclusion: Treatment with lexipafant and monoclonal antibodies against ICAM-1 or PECAM-1 reduced the severity of pancreatitis-associated gut endothelial dysfunction, and decreased systemic concentrations of IL-1 and local leucocyte recruitment.

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Introduction

Pancreatitis-associated gastrointestinal dysfunction is characterized by pancreatic and peripancreatic infection caused by bacteria of mainly enteric origin. Intestinal complications in pancreatitis include motility disturbance, inflammatory alterations, stenosis, ischaemia, necrosis and perforation[1–4]. Enteric bacteria have been reported to predominate in pancreatitis-associated infections, contributing to the high mortality rate in patients with severe acute pancreatitis[5,6]. Experimental studies have demonstrated that intestinal dysfunction during acute pancreatitis results in translocation of enteric bacteria to the systemic circulation and extraintestinal sites (gut origin sepsis)[7,8]. Potential mechanisms by which enteric bacteria pass through the intestinal barrier include impaired intestinal motility, disturbed enteric bacterial ecology, increased adhesion of pathogenic bacteria on the surface of mucosal epithelial cells, mucosal endothelial barrier dysfunction, overactivation of local macrophages, decreased systemic immune defence function, mucosal ischaemia and poor oxygen extraction[6,9,10].

Endothelial barrier dysfunction probably plays an important role in the pathogenesis of both the systemic inflammatory response syndrome and multiple organ dysfunction syndrome (MODS), by exposing adhesion molecules on the surface of endothelial membranes, producing and releasing inflammatory mediators, interacting with circulating leucocytes and compromising mucosal barrier integrity[11]. Plasma extravasation resulting from increased endothelial permeability is a critical characteristic of endothelial barrier dysfunction, associated with tissue oedema, leucocyte recruitment and organ dysfunction. Inflammatory mediators produced and released during acute pancreatitis may not only be early markers of disease severity but also critical links in the pathogenesis and pathophysiology of the disease. Such mediators include interleukins, enzymes released from polymorphonuclear leucocytes, oxygen free radicals, platelet-activating factor (PAF) and adhesion molecules[11]. In the present study, the potential therapeutic inhibition of PAF, intercellular adhesion molecule (ICAM) 1 (CD54) and platelet endothelial cell adhesion molecule (PECAM) 1 (CD31) was investigated in pancreatitis-associated gut endothelial barrier dysfunction in rats, by using a PAF antagonist (lexipafant, BB-882) and monoclonal antibodies against rat ICAM-1 and PECAM-1. Alterations in gut endothelial function and leucocyte recruitment, and serum concentrations of interleukins were evaluated.

Materials and methods

Adult male Sprague–Dawley rats, weighing about 250 g, were fed standard rat chow (R3; Astra-Ewos, Södertälje, Sweden) and water *ad libitum*. The rats were allowed to acclimatize to laboratory conditions for 4–6 days and were subjected to a 12-h day/night cycle living in stainless-steel mesh cages (three rats per cage) at constant temperature (22 °C). The protocol was approved by the Animal Ethics Committee at Lund University. All animals were handled in accordance with the guidelines set forth by the Swedish Physiological Society.

The rats had surgery under aseptic conditions using ether anaesthesia. Acute haemorrhagic pancreatitis was induced by intraductal administration of 0·2 ml glycylglycin–sodium hydroxide buffer 0·025 mol/l (pH 8 0) containing 5 per cent sodium taurodeoxycholate, by the use of an infusion pump at a speed of 0·04 ml/min, following clamping of the proximal end of the common bile duct and cannulation of the biliary–pancreatic duct with a thin polyethylene catheter (0·66 mm outer diameter; Portex, Hythe, UK). The solution of sodium taurodeoxycholate was sterilized at 100 °C for 20 min before use. Sham-operated controls had an identical laparotomy and isolation of the common bile duct, but without taurodeoxycholate injection.

The animals were randomly allocated into five groups: (1) control group, consisting of animals subjected to sham operation with saline, lexipafant ((S)-4-methyl-2-{methyl-[4-(2-methyl-imidazo{4,5-c}pyridin-1-ylmethyl)-benzene-sulphonyl]-amino}pentanoic acid ethyl ester; BB-882, British Biotech, Oxford, UK) or antibodies against ICAM-1 and PECAM-1 ($n = 4$ each); (2) acute pancreatitis with saline; (3) acute pancreatitis with lexipafant; (4) acute pancreatitis with monoclonal antibody against rat ICAM-1 (anti-ICAM1-Mb) purified from ascites on a Protein A matrix (R & D Systems, Minneapolis, Minnesota, USA); and (5) acute pancreatitis with monoclonal antibody against rat PECAM-1 (anti-PECAM1-Mb) purified from tissue culture supernate on a Protein A matrix (R & D Systems). There were six surviving animals in each treated pancreatitis group. Sterile saline or saline containing anti-ICAM1-Mb 0·5 mg/kg, anti-PECAM1-Mb 0·5 mg/kg or lexipafant 5 mg/kg in a volume of 0·2 ml was injected intraperitoneally 30 min after sham operation or induction of pancreatitis. Measurements were performed 12 h after induction of acute pancreatitis or sham operation.

Measurement of capillary endothelial permeability

Red blood cells (RBCs) were labelled with ^{51}Cr (New England Nuclear, Boston, Massachusetts, USA) for 20 min at room temperature and then washed twice with physiological saline. The radioactivity was about $1{\cdot}5 \times 10^6$ c.p.m. per ml. Distal small intestinal and colonic endothelial permeability was assessed in rats by the passage of ^{125}I-radiolabelled human serum albumin (HSA; Institutt for engergiteknikk, Kjeller, Norway) from blood to the tissues. ^{125}I-labelled HSA in 1 ml (10^6 c.p.m.) was injected into the femoral vein. After equilibration for 1 h, 1 ml blood was drawn from the femoral vein, followed by injection of ^{51}Cr-radiolabelled RBCs (10^5 c.p.m. per ml). The animals were sacrificed by an overdose of ether 2 min after the RBC injection. ^{125}I and ^{51}Cr in blood and tissue samples was measured in a γ counter (1272 Clinigamma; LKB, Wallac, Finland) after which the wet tissue weight of each sample was determined.

Capillary endothelial permeability was assessed by leakage of the radioisotope from blood into the tissues and expressed as isotopic flux, defined as the proportion of ^{125}I radioactivity per gram of tissue compared with per gram of blood as described previously[12]. To assay possible redistribution of tissue blood, tissue blood content was calculated by the proportion of ^{51}Cr counts per gram of tissue and ^{51}Cr counts per gram of blood. To correct for potential differences in the vascular surface area available for exchange of albumin, the albumin leakage index was calculated by dividing the extravascular protein accumulation in each tissue by assuming that all ^{51}Cr-labelled RBCs remained intravascular, using the formula: albumin leakage index = (extravascular tissue ^{125}I counts/^{125}I counts per gram blood)/tissue blood content. Tissue blood content was calculated as ^{51}Cr-radiolabelled RBC counts per gram tissue/^{51}Cr-labelled RBC counts per ml blood. Extravascular tissue ^{125}I count was obtained by the subtraction of ^{125}I counts per gram of blood sample multiplied by tissue blood content from ^{125}I counts per gram of tissue.

Assay of interleukins

Serum levels of interleukin (IL) 1β and IL-6 were determined by an enzyme-linked immunosorbent assay. Antibodies specific for rat IL-1β and IL-6 were coated on to the wells of the microtitre strips provided (BioSource International, Camarillo, California, USA). The samples, including standards of known rat IL-1β and IL-6 content (BioSource), were pipetted into the wells, incubated and washed. The intensity of the coloured product generated by the streptavidin–peroxidase system was measured at 450 nm wavelength with a spectrophotometer, and was directly proportional to the concentration of IL-1β and IL-6. The sensitivity of this method was more than 90 pg/ml as the limit of detection of the assay and the intra-assay and interassay variance was less than 10 per cent of the mean values.

Measurement of leucocyte recruitment

The intestine was perfused with heparinized phosphate-buffered saline (PBS) to exclude tissue blood and the samples were harvested, frozen immediately in liquid nitrogen and stored at − 70 °C pending further analysis. The samples (100–200 mg) were weighed, put in ice-cold potassium phosphate buffer 20 mmol/l (pH 7·4) and homogenized for 30 s. The suspension was centrifuged at 10 000 r.p.m. for 15 min at 4 °C, after which the supernatant was discarded to prevent interference by haemoglobin. The precipitates were rehomogenized with PBS 50 mmol/l containing 0·5 per cent hexadecyltrimethylammoniumbromide and ethylenediamine tetra-acetic acid 10 mmol/l, followed by sonicating, freezing, thawing and homogenizing twice in order to permeate cellular membranes. The reaction was terminated with sodium acetate 0·2 mol/l (pH 3·0), after incubation for 3 min at 37 °C with a reaction solution containing 0·5 per cent hexadecyltrimethylammoniumbromide, 3,3′,5,5′-tetrametylbenzidine 1·6 mmol/l and hydrogen peroxide 0·3 mmol/l in PBS 80 mmol/l (pH 5·4)[13]. Tissue leucocyte recruitment was reflected by the myeloperoxidase (MPO) activity, defined as the change in absorbance at 655 nm per min.

Statistical analysis

Unpaired two-tailed Student's *t* test or a non-parametric test (Mann–Whitney rank sum test) was used after analysis of variance. $P < 0{\cdot}05$ was considered significant. Values are expressed as mean(s.e.m.).

Results

Two animals with pancreatitis treated with saline (two of eight) and one with pancreatitis treated with anti-ICAM1-Mb (one of seven) died within the experimental period; there were no deaths in the other groups. The HSA leakage index significantly increased both in the distal small intestine and colon in animals with pancreatitis treated with saline, compared with controls (*Fig. 1*; $P < 0{\cdot}05$ and $0{\cdot}01$ respectively). The HSA leakage index in the distal small intestine in animals with pancreatitis treated with lexipafant or anti-ICAM1-Mb was lower than that in animals with pancreatitis that received saline. The

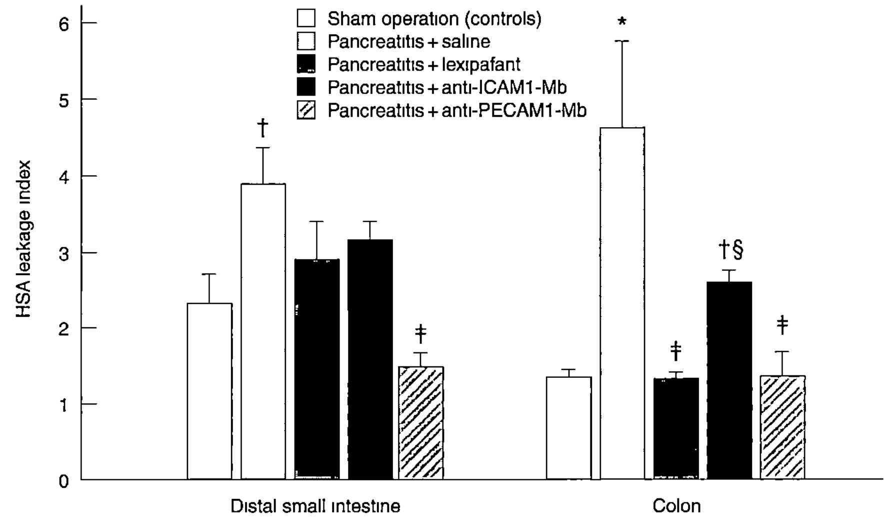

Fig. 1 Mean (s.e.m.) human serum albumin (HSA) leakage index in the ileum and colon 12 h after sham operation or induction of acute pancreatitis. *$P < 0{\cdot}01$, †$P < 0{\cdot}05$ *versus* control animals; ‡$P < 0{\cdot}01$, §$P < 0{\cdot}05$ *versus* animals with pancreatitis treated with saline ($n = 6$ surviving rats). Analysis of variance and Mann–Whitney rank sum test

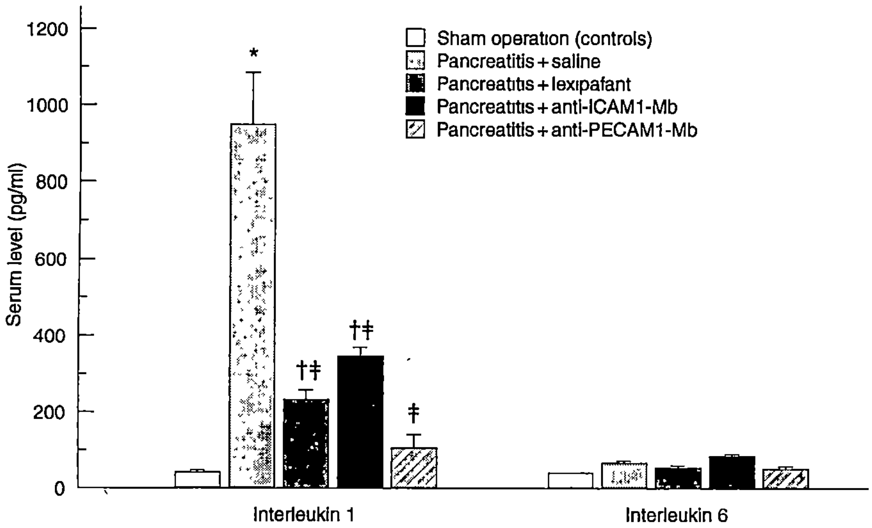

Fig. 2 Mean (s.e.m.) serum levels of interleukin (IL) 1 and IL-6 12 h after sham operation or induction of acute pancreatitis in animals. $^*P < 0\cdot01$, $^\dagger P < 0\cdot05$ *versus* control animals, $^\ddagger P < 0\cdot01$ *versus* animals with pancreatitis treated with saline ($n = 6$ surviving rats). Analysis of variance and Student's *t* test

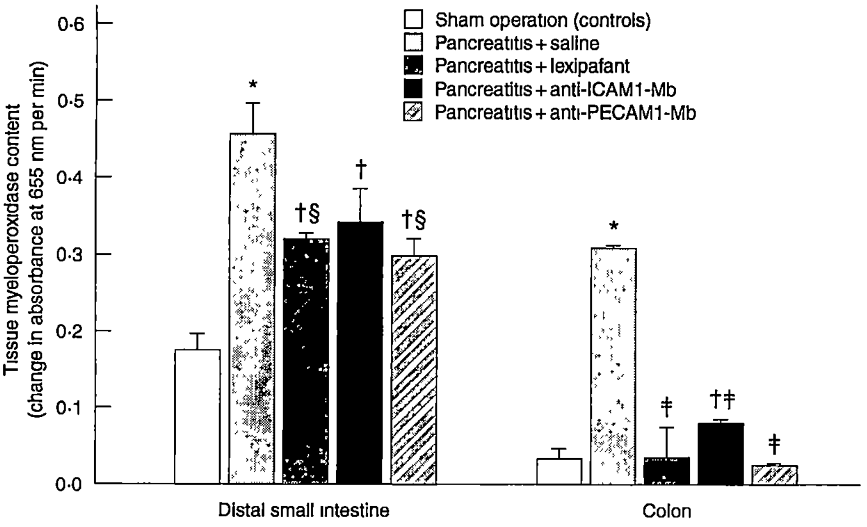

Fig. 3 Mean (s.e.m.) tissue myeloperoxidase content in the ileum and colon 12 h after sham operation or induction of acute pancreatitis. $^*P < 0\cdot01$, $^\dagger P < 0\cdot05$ *versus* control animals; $^\ddagger P < 0\cdot01$, $^\S P < 0\cdot05$ *versus* animals with pancreatitis treated with saline ($n = 6$ surviving rats). Analysis of variance and Student's *t* test

colonic HSA leakage index decreased significantly in animals with pancreatitis after treatment with lexipafant ($P < 0\cdot01$) or anti-ICAM1-Mb ($P < 0\cdot05$), compared with that in animals treated with saline. The HSA leakage index in colon in animals with pancreatitis treated with anti-ICAM1-Mb was significantly higher than that in control animals ($P < 0\cdot05$). The index in the distal small intestine and colon in animals with pancreatitis treated with anti-PECAM1-Mb was significantly lower than that in animals with pancreatitis treated with saline ($P < 0\cdot01$), but not significantly different from that in control animals.

Serum levels of IL-1 in animals with pancreatitis and saline increased significantly to about 1000 times that seen in controls ($P < 0\cdot01$; *Fig. 2*). IL-1 levels were significantly lower in animals with pancreatitis treated with lexipafant, anti-ICAM1-Mb or anti-PECAM1-Mb ($P < 0\cdot05$). Serum levels of IL-6 in animals with pancreatitis treated with lexipafant and anti-ICAM1-Mb were significantly higher than those in control animals ($P < 0\cdot01$). Serum levels of IL-6 in all experimental animals were less than the limit of detection of the assay (less than 94 pg/ml).

Tissue leucocyte recruitment, assessed by MPO content, significantly increased in the distal small intestine and colon after induction of acute pancreatitis and treatment with saline (*Fig. 3*; $P < 0\cdot01$ *versus* controls). Treatment with lexipafant or anti-PECAM1-Mb significantly decreased tissue MPO content in the distal small intestine after induction of pancreatitis ($P < 0\cdot05$ *versus* animals with pancreatitis treated with saline), although levels were significantly higher than those in controls. MPO content in the colon in animals with pancreatitis after treatment with lexipafant, anti-ICAM1-Mb or anti-PECAM1-Mb was significantly lower than that in animals treated with saline ($P < 0\cdot01$). Colonic MPO content in animals with pancreatitis treated with anti-ICAM1-Mb was still significantly higher than that in control animals.

Discussion

Pancreatitis-associated gut barrier dysfunction has been characterized by the passage of enteric bacteria through the mucosal barrier to extraintestinal sites (bacterial translocation), impaired intestinal motility and increased intestinal permeability[5,6,9,14]. Alterations in intestinal permeability are noted in mucosal barrier dysfunction in a variety of conditions associated with the development of MODS[15]. Endothelial barrier dysfunction, with increased endothelial permeability, release of inflammatory mediators and exposure of adhesion molecules on the cellular surface, plays an important role in development of MODS[11]. The maintenance of gut endothelial barrier integrity is critical for the prevention of secondary gut barrier dysfunction[16]. In the present study, pancreatitis-associated intestinal endothelial barrier dysfunction was measured by the leakage of radiolabelled albumin. Acute haemorrhagic pancreatitis induced by 5 per cent sodium taurodeoxycholate has a 100 per cent mortality rate within 24–48 h[12]. A previous study showed that intravenous administration of a mouse monoclonal antibody (immunoglobulin G_1) directed against rat ICAM-1 resulted in optimal protection against ischaemia–reperfusion-induced tissue injury and animal death at a dose of 0·5–5·0 mg per kg body-weight[17]. The 0 5-mg dose by intraperitoneal administration was selected for the present study, and 50 per cent of antibodies labelled with radioisotope appeared in the circulation 30–60 min after administration (data not shown). Treatment with lexipafant, anti-ICAM1-Mb or anti-PECAM1-Mb reduced, to varying degrees, the severity of pancreatitis-associated gut endothelial barrier dysfunction. The effect of treatment with the PAF antagonist and adhesion molecule antibodies depended on the time of treatment, i.e. 30 min, 1 h and 3 h after induction of acute pancreatitis (data not shown).

Leucocyte–endothelial cell interaction leads to excessive movement of leucocytes to the tissues, as well as endothelial barrier compromise, responsible for initiation of the inflammatory reaction, serious tissue injury and organ dysfunction. Leucocyte recruitment involves transient tethering and rolling of leucocytes along endothelial cells, triggering of signals that activate upregulation of leucocyte function, tight adhesion of leucocytes to the vascular endothelium and transendothelial migration[18]. PAF is a biologically active phospholipid stored in its precursor form within cell membranes. It can act as an intercellular signal responsible for cell communication and an inflammatory mediator involved in the pathogenesis of inflammation. Major contributions of PAF during the inflammatory reaction include acting as an inflammatory stimulator to the leucocyte system, causing leucocyte rolling on the endothelium, adhesion and passage through interendothelial cells to the interstitium[19,20]. ICAM-1 (CD54) is an adhesion receptor of the immunoglobulin superfamily expressed on endothelial cells. It functions as a counter-receptor of lymphocyte function-associated antigen 1 (CD11a/CD18) and Mac-1 (CD11b/CD18) present on leucocytes. ICAM-1 is predominantly involved in leucocyte tethering, rolling and tight adhesion on to vascular endothelial cells, and partially in leucocyte migration[18]. PECAM-1 (CD31), during leucocyte–endothelial cell interaction, may control the triggering of signals and leucocyte migration between interendothelial cells[21]. However, the potential value of treatment with adhesion molecule antibodies in pancreatitis-induced distant organ/tissue dysfunction is not known.

The present study demonstrated that treatment with lexipafant, anti-ICAM1-Mb or anti-PECAM1-Mb after induction of acute pancreatitis diminished gut leucocyte recruitment, expressed by tissue MPO content, in parallel with restoration of endothelial barrier function. It may be that lexipafant blocks PAF receptors on the surface of endothelial cells, thus reducing circulating PAF and so downregulating the activation of leucocytes/macrophages and the interaction between leucocytes and endothelial cells, and maintaining the integrity of the endothelial barrier. In the present study, anti-ICAM1-Mb was less effective than lexipafant or anti-PECAM1-Mb against gut leucocyte recruitment and plasma exudation in both the distal small intestine and colon of animals with pancreatitis. It could be that other adhesion molecules, such as vascular cell adhesion molecule 1, ICAM-2 and mucosal cell adhesion molecule 1, have similar functions to ICAM-1, and/or that there is greater expression of ICAM-1 compared with other mediators after induction of pancreatitis. Treatment with anti-PECAM1-Mb had the most pronounced effect in reducing plasma extravasation and local MPO content, probably owing to a decrease in production and release of intercellular signals during leucocyte–endothelial cell interaction and blockage of leucocyte migration through interendothelial junctions.

Adhesion of inflammatory cells to endothelial cells, and the resulting endothelial barrier dysfunction and organ failure is associated with a variety of inflammatory mediators and/or cytokines[11]. Cytokine-regulated expression of E-selectin, ICAM-1 and vascular cell adhesion molecule 1 in cultured human intestinal microvascular endothelial cells demonstrated a dose-dependent and a time-related response[19]. Alterations in cytokine levels have been suggested to be essential in the pathogenesis of both the local and systemic inflammatory response in acute pancreatitis[20]. The present study demonstrated a correlation between plasma levels of IL-1, local leucocyte recruitment (MPO content) and exudation of plasma albumin into the interstitium. Treatment with lexipafant, anti-ICAM1-Mb and anti-PECAM1-Mb reduced the pancreatitis-induced increase in plasma levels of IL-1 12 h after induction of pancreatitis, although levels still were higher than those in sham-operated animals. Levels of IL-6 were below the detection limit in experimental animals, which implies that IL-6 is not involved this early in pancreatitis. Clinical data showed that levels of the IL-1 receptor antagonist were 15 times higher than those of IL-6 and 150 times higher than IL-8 levels at the early stage of severe acute pancreatitis[22], indicating that alterations in the IL-1 and anti-IL-1 patterns may play a central pathophysiological role in acute pancreatitis. IL-1 could compromise endothelial barrier integrity by either overactivating leucocytes, initiating the release of inflammatory mediators (oxygen-free radicals and nitric oxide) from leucocytes and endothelial cells, or enhancing the interaction between these cells. On the other hand, compromised endothelial cells can increase the synthesis and secretion of IL-1. The endothelial-dependent effect of IL-1 has been suggested to be important in the development of secondary pancreatic infections[6].

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Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland

The following abstracts were presented to the annual meeting of the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland on 24–25 September 1998. The British Journal of Surgery prize was awarded to Miss J. Blazey.

Early and long-term results after necrosectomy for necrotizing pancreatitis

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Background: Necrotizing pancreatitis is a difficult clinical problem associated with significant mortality and morbidity rates Indications for surgical intervention, and the timing and type of intervention, remain controversial issues. A 10-year experience in the management of this condition in a tertiary referral centre is reviewed; treatment policies and early and long-term results are reported.

Methods: Between 1987 and 1997, 39 consecutive patients (32 men, seven women), with a mean age of 47 (range 13–74) years, underwent necrosectomy for severe necrotizing pancreatitis. Diagnosis was confirmed by contrast-enhanced computed tomography. Twenty-nine patients were referred from other hospitals in Northern Ireland. The aetiology included gallstones (15), alcohol (ten), idiopathic (seven), surgery (two), endoscopic retrograde cholangiopancreatography (two), blunt trauma (one), hyperlipidaemia (one) and pancreas divisum (one). Mean Acute Physiology And Chronic Health Evaluation (APACHE) II score on admission or arrival was 2 (range 5–21). Indications for surgical intervention were clinical deterioration with development of multiple organ failure, despite maximal medical support in the intensive care unit (ICU), or positive fine-needle aspiration for micro-organisms or radiographic evidence of infected necrosis (i.e. presence of gas within peripancreatic collection). The mean interval from onset to intervention was 23 (range 9–47) days. In 13 patients a conventional approach (necrosectomy with primary closure over drains) was used, 14 patients underwent planned staged necrosectomy with delayed closure over drains and in 12 patients necrosectomy with open laparostomy was undertaken.

Results: There were five deaths and 14 patients experienced significant hospital morbidity (fistula, ten, pseudocyst, two; renal failure, two). Variables which correlated with mortality rate were higher APACHE II score, acute renal failure requiring dialysis and early intervention. There was no difference in either mortality or morbidity rate between infected and sterile necrosis, or between the three surgical techniques Long-term morbidity occurred in 20 surviving patients (incisional hernia, ten; endocrine pancreatic insufficiency, nine; exocrine pancreatic insufficiency, two; pseudocyst, two, chronic renal failure, two; recurrent pancreatitis, one; and chronic pain, one)

Conclusion: A low mortality rate can be achieved in patients with severe necrotizing pancreatitis with aggressive surgical intervention. Early maximal medical treatment and ICU support is essential before intervention, which should preferably be avoided early in the course of the disease and should be based on well defined criteria The long-term morbidity rate remains high, although not always severe. This emphasizes the need for close follow-up.

Prevalence of R117H mutation in the cationic trypsinogen gene in patients with hereditary pancreatitis

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Background: The R117H mutation of the cationic trypsinogen (CT) gene (G to A mutation in exon 3), located on chromosome 7q35, is one of the known mutations that is linked to hereditary pancreatitis (HP) and is thought to alter a trypsin recognition site responsible for the breakdown of inappropriately activated trypsinogen so resulting in pancreatitis The aim of this study was to determine the prevalence of this mutation in patients with HP and to correlate presence of the mutation with disease characteristics.

Methods: Polymerase chain reaction amplification of the third exon of the CT gene was performed on blood DNA This was digested by the restriction endonuclease Afl III and fragments were sized by agarose gel electrophoresis Haplotype analysis was carried out using three short tandem repeat markers in the region of the CT gene.

Results: Seven discrete families with HP (three to seven generations) were identified (22 affected individuals). The mutation was present in individuals from three of the seven families. It was absent in all affected individuals from the other four families. A higher proportion of patients requiring pancreatic surgery was seen in families expressing this mutation (eight of 14 *versus* one of eight, $P = 0·016$). Mean(s.d.) age of onset was similar in both groups (7·9(5·8) *versus* 6·3(10·1) years, $P = 0·13$). In the affected families, the same high-risk haplotype was present in two families, suggesting a common ancestor. The third family carried a unique haplotype.

Conclusion: A single G to A mutation in the third exon of the CT gene was found in three families with HP originating from this region and appears to be associated with more severe disease. Further work is being undertaken to analyse the CT gene more fully in families in which this common first mutation was not identified

Laparoscopic bile duct injuries: a single-institution experience spanning 8 years

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Background: This audit represents the authors' experience in the management of 42 bile duct injuries following laparoscopic cholecystectomy and is the largest series reported so far in the UK.

Methods: Between November 1990 and May 1998, 42 patients were referred for management of bile duct injury following laparoscopic cholecystectomy. The case notes of all patients were reviewed and follow-up information was obtained to provide a 100 per cent follow-up rate. Aspects of the cholecystectomy, presentation, investigation, definitive treatment and follow-up are discussed.

Results: The referral source was 25 surgeons from 17 different hospitals. The incidence peaked in 1992 (ten cases) and has been stable at four referrals per year over the past 4 years. The median age was 56 years and the M : F ratio 10 : 32. Thirty-five laparoscopic operations were performed by consultants and seven by trainees. Intraoperative cholangiography was performed in three. Seventeen operations were converted to an open procedure because of intraoperative difficulty. Injury was noted at operation in nine and an immediate restorative procedure was attempted. Twelve patients had had a reconstructive procedure before referral to this unit and the remainder were referred with a fresh injury. Patients in whom the bile duct was transected (n = 34) presented mostly with jaundice; those with minor injuries not involving the common duct (n = 8) presented with peritonitis. Thirty patients required operation; 25 underwent hepaticojejunostomy reconstruction, two needed revision of a previous biliary–enteric anastomosis, two had primary bile duct repair over a T tube and one required relaparoscopy to clip a leaking cystic duct. At a median of 12 months four patients who had had a reconstruction were symptomatic for cholangitis. Percutaneous transhepatic dilatation was successful in two and a further two required revision of the anastomosis. Another four patients had asymptomatic stenosis and were treated successfully by a single episode of dilatation. Follow-up showed all patients to be asymptomatic at a median follow-up of 42 months; however, six had a raised level of alkaline phosphatase. The remaining patients were managed successfully by therapeutic endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography. The overall median hospital stay was 18 days. Perioperative complications were seen in nine patients with no procedure-related deaths.

Conclusion: Although the initial learning curve seems to have been overcome, a steady state of problems now exists and seems likely to continue. Best results were obtained by hepaticojejunostomy. Most postrepair strictures were dealt with without operation.

Surgical impact of adhesions following surgery in the upper abdomen

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Background: The Surgical and Clinical Adhesions Research (SCAR) study set out to determine the long-term morbidity associated with postoperative adhesions following open abdominal and pelvic surgery, including the burden associated with adhesions after surgery in the upper abdomen.

Methods: Scotland's National Health Service hospital admissions are recorded by the Scottish Medical Record Linkage system. This system allows detailed analysis of hospital activity throughout Scotland including follow-through of individual patients, with sophisticated accuracy checks to ensure the quality and totality of the data set. Within the SCAR study, the total number of individuals who underwent an open abdominal or pelvic procedure in 1986 was defined, a subset of whom underwent surgery in the anatomical area of the upper abdomen (fore gut and related organs). Disease (International Classification of Diseases version 9) and procedure (Office of Population Censuses and Surveys 3/4) codes for adhesion-related problems or reoperations that might be complicated by the presence of adhesions were identified. For the purposes of the study only readmissions for directly related adhesion complications during the following 10 years were considered (e.g. small bowel obstruction and adhesiolysis). The study was steered by a multidisciplinary panel of surgeons, gynaecologists and health economists.

Results: In 1986 in Scotland, a total cohort of 8714 patients had open surgery in the upper abdomen which was considered likely to cause adhesions. This compared to 12 585 undergoing open surgery in the lower abdomen (mid hindgut) and 8489 in the female reproductive tract. The majority of patients in this cohort underwent open surgery on the gallbladder (44·4 per cent) or stomach (20·6 per cent). During the 10-year study 3293 individuals (37·8 per cent) required one or more readmissions for surgical or medical treatment for conditions either related to adhesions or involving a reoperation which could be complicated by adhesions. In total, 7048 surgical or medical readmissions were identified, with a mean of 2·1 readmissions per patient. At least 321 (4·6 per cent) of these readmissions were a direct result of abdominal or pelvic adhesions, constituting a large clinical burden. Analysis of readmissions over time showed that this burden continued steadily over the 10-year study period. As well as this workload burden, there was a risk for the patient associated with open surgery on the foregut with a mean of 3·7 readmissions for direct adhesion complications for every 100 initial procedures. This rate varied according to the site of initial surgery 3·0 per 100 procedures for open surgery of the gallbladder, 3·5 per 100 for the stomach and 7·3 per 100 for open surgery on the pancreas.

Conclusion: The SCAR study provides the first epidemiological assessment of postoperative adhesions. Using an extremely conservative view, the medical and surgical impact following open surgery in the upper abdomen is considerable with 4·6 per cent of readmissions over a 10-year period directly attributable to adhesions. The full impact of adhesions, including their effect on subsequent surgery, is likely to be considerably greater and extensive research is being progressed with the SCAR data set to investigate further the burden and associated costs, and optimum strategies to reduce the problem.

Prospective study examining differences in quality of life between patients surviving 2 years after oesophagectomy and patients dying within 2 years of surgery

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Background: Quality of life (QL) measurement is important for patients with oesophageal cancer but longitudinal studies may contain a bias because assessments only include healthy survivors who are able to complete questionnaires. This study examined QL in patients undergoing oesophagectomy by comparing results from those surviving 2 years after operation with results from patients dying within 2 years.

Methods: Between November 1993 and May 1995, 52 patients (36 men; mean age 67 years) underwent oesophagectomy. Prospective QL assessments were performed with the European Organisation for Research on Treatment of Cancer QLQ-C30 and the dysphagia scale from the oesophageal cancer module before treatment, 6 weeks, 3, 6, 9 and 12 months after operation, and at 6-month intervals thereafter, for a minimum of 3 years after operation. Mortality and morbidity rates and survival data were recorded.

Results: Two years after operation, 17 patients (33 per cent) were alive (group 1) and 35 had died (group 2). Groups were comparable for age, sex, tumour histology and length, dysphagia grade and performance scores. Six weeks after surgery patients in group 1 had worse functional, symptom and global health QL scores than before treatment. These subsequently improved such that by 9 months after operation most QL scores had returned to preoperative levels, except for persisting problems with dyspnoea and diarrhoea. Six weeks after operation patients in group 2 also reported worse QL in all domains, but this never recovered. Six months after treatment patients in group 2 had significantly worse physical, role, emotional and social function than those surviving 2 years and significantly more problems with appetite loss ($P < 0{\cdot}001$). The notable exception in both groups was dysphagia, which improved after operation. This improvement was maintained until death or for the duration of the study.

Conclusion: Patients dying within 2 years of operation suffer an irreversible loss of QL, except that dysphagia is relieved. Further work is needed to assess whether additional postoperative support or the use of multimodality adjuvant treatment can improve the outcome for this group of patients.

Prediction of need for multiple dilatations after cervical oesophagogastrostomy

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Background: The aim of this study was to investigate the frequency of anastomotic stricture formation after subtotal oesophagectomy with cervical oesophagogastrostomy.

Methods: Patients undergoing surgery over a 3-year period using an identical handsewn single-layer anastomotic technique were studied Details of the operations, complications and need for anastomotic dilatation were recorded.

Results: Sixty-two patients (41 men) with a mean age of 64 (range 36–90) years were included. Fifty-eight underwent surgery for carcinoma, two for stromal tumours, one for achalasia and one for Crohn's disease. Thirty-two (2 per cent) developed a benign anastomotic stricture requiring a median of 4 (range 1–22) dilatations. The median time from operation to first dilatation was 50 days. There was a significant correlation between the time to first dilatation and the total number of dilatations ($P = 0{\cdot}006$). Patients who developed symptomatic strictures within 30 days of operation required a median of 9·5 dilatations compared with 3·5 in those who presented beyond this time ($P = 0{\cdot}01$). The development of a clinical leak significantly increased the number of dilatations required, from a mean of 5·2 to 10·4 ($P = 0{\cdot}04$).

Conclusion: The incidence of benign anastomotic stricture formation requiring dilatation after cervical oesophagogastrostomy is about 50 per cent. Patients who require dilatation within 30 days of surgery to restore swallowing to normal are likely to require the procedure on multiple occasions and should be counselled accordingly.

Tonometric measurement of gastric intramucosal pH following oesophagectomy predicts postoperative complications

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Background: Gastric mucosal hypoperfusion can be assessed tonometrically by measuring the gastric intramucosal pH (pH_i); its ability to predict outcome in the critically ill has been demonstrated previously. This study employed the new technique of recirculating gas tonometry to measure gastric $\mathrm{pH_i}$ following oesophagectomy; its ability to predict anastomotic complications was tested, since ischaemia at the oesophagogastric anastomosis is thought to be an important factor in their aetiology.

Methods: A gastric tonometer was placed in the gastric tube of 28 consecutive patients undergoing oesophageal resection. They were connected to a Tonacap analyser (Datex-Engstrom Division, Instrumentarium Corporation, Helsinki, Finland) which automatically samples gas from the intragastric tonometer balloon and measures the carbon dioxide concentration within it. In conjunction with simultaneously taken arterial blood samples, gastric $\mathrm{pH_i}$ was calculated at the end of the operation and then at 12-h intervals for up to 48 h after operation. Patients who survived were followed for 3 months and all postoperative complications were recorded. Statistical comparison was made using the independent samples *t* test.

Results: Eight patients suffered an anastomotic leak or benign stricture after operation; five others had a life-threatening complication not thought to be related to the anastomosis, of whom two survived. Over the first 24 h after operation median gastric $\mathrm{pH_i}$ was lower at all three measurement points in the complication group than in the no complication group ($P > 0{\cdot}05$ in all cases). However, at 36 and 48 h there were significant differences (in both cases $P < 0{\cdot}01$), at these times median (range) $\mathrm{pH_i}$ in the complication group was 7·19 (7·00–7·24) and 7·20 (7·03–7·49) respectively, and in the no complication group 7·28 (7·12–7·39) and 7·32 (7·25–7·44). A mean $\mathrm{pH_i}$ at 36 and 48 h after operation of 7·25, with both measurements less than this value as a discriminating coefficient, was employed. This had a sensitivity of 92 per cent and a specificity of 92 per cent for predicting all complications. Applied specifically to anastomotic complications the sensitivity was 100 per cent and specificity 92 per cent.

Conclusion: Gastric $\mathrm{pH_i}$ is easily measured after operation using recirculating gas tonometry. By taking measurements at 36 and 48 h, it appears possible to predict postoperative complications following oesophagectomy and the technique may provide a useful adjunct to the monitoring of these patients.

Diagnosis and staging of pancreatic carcinoma: comparison of manganofodipir trisodium-enhanced magnetic resonance imaging and dynamic contrast-enhanced spiral computed tomography

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Background: The efficacy of manganofodipir trisodium (MnDPDP)-enhanced magnetic resonance imaging (MRI) and dual-phase dynamic contrast-enhanced spiral computed tomography (CT) in the diagnosis and staging of pancreatic carcinoma was compared.

Methods: Nineteen patients (eight men) aged 50–84 (mean 64) years with known or suspected pancreatic carcinoma were prospectively evaluated with MRI and CT. Precontrast T1 and T2 MRI sequences were supplemented by axial and coronal T1 images at 1·0 T, 20 min and 24 h following intravenous infusion of MnDPDP 0·5 ml/kg. Spiral CT was performed before contrast and dynamically after contrast during the pancreatic and portal venous phases of enhancement. The MRI and CT images were assessed independently by two observers blinded to the results of the other modality. The presence, site and size of any focal pancreatic mass were recorded and potential resectability was assessed by evaluating extraglandular extension, vascular involvement, lymphadenopathy, peritoneal spread and presence of hepatic metastases. Findings on MRI and CT were compared with the findings at surgery.

Results: Pancreatic adenocarcinomas were diagnosed histologically in 15 of 19 patients. MRI and CT each identified all of the proven malignancies. Clear evidence of irresectability with liver metastases or vascular invasion was identified in six of 15 patients at MRI, who did not therefore go on to surgery. In one of these six patients the CT findings were equivocal. Nine of the 15 patients went on to laparoscopy ($n = 2$) or laparotomy ($n = 7$). Of these nine patients seven were correctly assessed as resectable or irresectable on MRI and six by CT. The overall accuracy for assessing resectability was therefore 87 per cent for MRI and 73 per cent for CT. Liver metastases were confidently identified in three of 15 patients on both MRI and CT. Two patients with indeterminate liver lesions on CT were shown to have only benign liver lesions (cysts or haemangiomas) on MRI.

Conclusion: MnDPDP-enhanced MRI performed slightly better than dual-phase dynamic contrast-enhanced CT in the preoperative assessment of pancreatic tumour resectability. MRI also appears to offer an advantage in the evaluation of associated focal liver lesions.

Laparoscopic ultrasonography is accurate for staging large pancreatic tumours

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Background: The accuracy of laparoscopic ultrasonography in staging pancreatic and periampullary tumours in a referral unit was determined and its use for the subgroup of tumours of stage T_3 or greater was assessed.

Methods: From a larger series of staging laparoscopies 22 patients with pancreatic lesions and five with periampullary tumours who were being considered for resection were staged with laparoscopy and laparoscopic ultrasonography. Only patients with computed tomography (CT) or magnetic resonance imaging (MRI) scans indicating potentially or equivocally resectable disease were included. The laparoscopist was blinded to the results of CT and MRI. Laparoscopy and laparoscopic ultrasonography were undertaken according to a standard protocol using a B & K Medical Diagnostic Ultrasound System 3535 with a colour flow Doppler module. Ascitic fluid was sent for cytology and metastatic disease was biopsied. Results were recorded on a pro forma which included an assessment of resectability. In the case of large tumours this included an assessment of the potential for a positive resection margin or the need for portal vein resection to obtain tumour clearance. The decision to pursue resection was made by the consultant surgeon, based on all the information available including that from laparoscopic ultrasonography. No patient was denied a surgical exploration on the basis of local irresectability determined only by laparoscopic ultrasonography. The predictions regarding resectability were compared with findings at open surgery and with histology.

Results: Assessment of irresectability by laparoscopic ultrasonography resulted in nine true positives, 16 true negatives, no false positives and one false negative. For pancreatic adenocarcinoma there were eight true positives, 13 true negatives and one false negative. Among the pancreatic group ten of 13 tumours correctly predicted as resectable were stage T_3 or greater (Union Internacional Contra la Cancrum, 1997). Of those predicted to be irresectable, all eight were T_3 or greater. Among this latter group three were predicted to be irresectable on the basis of local factors alone, two on the basis of metastatic disease alone and three on the basis of both local factors and metastases. Overall, for detection of irresectable disease laparoscopic ultrasonography had a positive predictive value of 100 per cent, a negative predictive value of 94 per cent and an accuracy of 96 per cent. Accuracy was 95 per cent for both the pancreatic tumour subgroup and the T_3 pancreatic subgroup.

Conclusion: Laparoscopic ultrasonography was accurate for predicting irresectability in this group of referred patients. The technique was also accurate for the subgroup with T_3 or greater pancreatic tumours.

Laparoscopic surgery for large hiatus hernia

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Background: The results of laparoscopic surgery for large symptomatic hiatus hernia were reviewed prospectively.

Methods: This was a prospective review of large (greater than 10 cm) hiatus hernias treated by laparoscopic surgery at the Royal Adelaide Hospital from January 1994 to July 1997. Demographic data, preoperative investigations, operative findings, operating times, conversion rate, complications and follow-up were recorded prospectively.

Results: Some 48 patients with a large hiatus hernia were treated laparoscopically. All had repair of the hiatal pillars and 47 had a fundoplication. The median age was 58 (range 30–87) years and there were 25 women. There were 11 sliding, eight paraoesophageal and 29 mixed hiatus hernias, and 20 completely intrathoracic stomachs. Median operating time was 75 (range 48–195) min and there were 12 conversions to an open operation; four because of difficulty reducing the hernia, three for obesity, two for bleeding, two because it was not possible to define the anatomy and one for gastric perforation. The majority of conversions occurred earlier in this experience and a change in technique to dissecting the sac out of the thoracic cavity reduced the conversion rate (38 to 15 per cent; $P = 0{\cdot}03$, Fisher's exact test). Complications occurred in eight patients and resulted in early reoperation in two (one open and one laparoscopic). There was no death. The median stay was 3 (range 2–10) days. At a median follow-up of 19 (range 3–46) months, eight patients had minor dysphagia and two patients had an incisional hernia (both converted to open operation). One patient had a recurrent paraoesphageal hernia at 6 months and required further surgery. Median satisfaction scores were 10 (range 7–10) of 10 and all patients said they would have the operation again.

Conclusion: Large hiatus hernias can be effectively treated laparoscopically. The initial high rate of conversion to open operation was reduced by a change in operative technique.

Presentation, management and outcome of oesophageal malignancy in patients aged over 75 years

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Background: Subjects over 75 years old constitute an increasing proportion of the general population and hitherto the management of most malignant diseases in this elderly group has been predominantly palliative. The aim of this study was to assess the mode of presentation, management and outcome of treatment in patients aged over 75 years presenting with oesophageal malignancy.

Methods: Data were collected prospectively from all patients aged over 75 years at presentation who were diagnosed at or referred to a single centre between October 1989 and May 1998. All patients underwent a full protocol of staging investigations and assessment of co-morbid disease. The main modality of therapy and its outcome were analysed, as was the overall survival. Statistical analysis was with the χ^2, Mann–Whitney and log rank tests.

Results: Eighty patients were studied (41 men). The median age at presentation was 82 (range 75–97) years. Adenocarcinoma was the predominant histological subtype (46, 58 per cent) compared with squamous cell carcinoma (SCC; 34, 42 per cent). Most patients were referred by a gastroenterologist (34 patients) or general practitioner (25). Dysphagia and weight loss were the commonest presenting symptoms (67 patients), with dyspepsia a significantly more frequent symptom for adenocarcinoma (22 of 46 *versus* six of 34, $P < 0{\cdot}05$). Patients with adenocarcinoma had more often received acid suppressing medication (20 of 46 *versus* seven of 34; $P < 0{\cdot}05$). The median duration of symptoms was 5 months and was significantly longer for adenocarcinoma than SCC (7 *versus* 4 months; $P < 0{\cdot}05$). Twenty-nine (26 per cent) of 80 patients were unfit for surgery mainly because of co-morbid cardiorespiratory disease, despite being staged as suitable for resection. A further 37 (46 per cent) were staged as having irresectable local disease or distant metastases and could not be offered surgery. Three patients declined surgery and two with high-grade dysplasia in Barrett's oesophagus remain under surveillance. Thirty-nine patients (49 per cent) were palliated with external beam and endoluminal radiotherapy, twenty-eight (35 per cent) had oesophageal dilatation and endoprosthesis insertion, two patients had no intervention and a further two had laser therapy. Nine (11 per cent) underwent Ivor–Lewis subtotal oesophagectomy with two-tier lymphadenectomy. The overall median survival for all modalities of therapy was 183 (95 per cent confidence interval 143–223) days. There was a significant survival benefit for those undergoing surgery compared with other options (402 *versus* 171 days; $P = 0\ 0204$). Survival following palliative measures was significantly better for radiotherapy than for dilatation and endoprosthesis insertion (214 *versus* 80 days, $P = 0{\cdot}0006$).

Conclusion: While surgical resection in selected patients offers the only chance of long-term survival, the advanced nature of oesophageal malignancy at presentation coupled with the high incidence of significant co-morbid disease precludes its use in most elderly patients. Thorough staging and careful assessment of overall fitness are crucial in identifying those suitable for surgery as well as establishing which palliative measures are most appropriate.

Oesophagectomy and total gastrectomy in a specialized district general hospital unit

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Background: The aim was to demonstrate that a low operative mortality rate (less than 5 per cent) is achievable for both oesophagectomy and total gastrectomy (TG) in a medium-sized district general hospital (DGH).

Methods: This was a prospective audit of all oesophagectomies and TGs performed in the first 5 years after establishment of a specialized upper gastrointestinal surgical–anaesthetic team.

Results: Some 82 procedures were undertaken, all by the same surgical team. Forty patients (median age 66 (range 41–76) years) underwent subtotal oesophagectomy (STO) using the two-stage approach Forty-two patients (median age 68 (range 35–80) years) underwent TG using a left thoracoabdominal approach in four and an abdominal approach in 38. There were no deaths in hospital or within 30 days for either procedure. Two patients in each group died within 90 days: one from myocardial infarction and one from paraneoplastic syndrome after STO, one from pulmonary embolism and one from malignant adhesive obstruction after TG. There was one anastomotic leak in each group. Four patients required a second procedure: for a postoperative bleed, a thoracic duct leak and a feeding jejunostomy (one patient each) after STO, and for drainage of a left subphrenic abscess after TG

Conclusion: It is reasonable to aim for an operative mortality rate of under 5 per cent for both STO and TG even in a DGH treating relatively small numbers of patients. Preoperative assessment and peroperative management by a single surgical–anaesthetic team, use of epidural analgesia and treatment in dedicated ward areas are all contributory factors. Clinical, audit and research links to the Northern Oesophago-Gastric Cancer Unit in Newcastle have ensured a uniformity of care across the region.

Carcinoma of the oesophagus and stomach in Wales: a 1-year survey

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Background: The management and outcome of patients presenting with oesophagogastric carcinoma over a 12-month period in Wales were reviewed.

Methods: Data were collected from September 1995 to September 1996 on 916 consecutive patients and submitted to confidential data analysis. The data originated from 20 hospitals and 70 surgeons treating these patients.

Results: The number of cases managed by each hospital varied between two and 124, and by each surgeon from one to 44. Three tumour sites were identified· carcinoma of the oesophagus ($n = 339$), carcinoma of the cardia (gastro-oesophageal junction; $n = 193$) and gastric carcinoma ($n = 384$) The 30-day mortality rate was 13 per cent for oesophageal carcinoma, 12 per cent for cardia carcinoma and 11 per cent for gastric carcinoma. Resection rates for the three tumour sites were 28, 44 and 56 per cent. There were 16 anastomotic leaks overall. For patients undergoing surgery, there was an inverse relationship between case load and mortality rate. This difference narrowed when ten or more patients were operated on per annum. For surgeons consulting with more than ten patients per annum and who operated on more than 70 per cent of these, the mortality rate was 18 per cent, compared with 5 per cent for those who operated on less than 70 per cent.

Conclusion: Numerically there is a broad range of experience amongst the surgeons who treat carcinoma of the oesophagus and stomach in Wales. There may be an optimum minimal case load and, with careful selection of patients for surgery, morbidity and mortality rates should be minimized

Transmural endoscopic drainage of pancreatic pseudocysts

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Background: Pancreatic pseudocysts requiring treatment for pain or obstructive symptoms may be drained by percutaneous or open surgical techniques. Endoscopic drainage has been reported in a few small series with short-term follow-up. The aim of this study was to determine the indications and success rates of transmural endoscopic drainage procedures.

Methods: All patients who presented over a 2-year period to a tertiary referral centre with pancreatic pseudocysts were included in the study. Endoscopic drainage was attempted using a side-viewing endoscope in patients with pseudocysts bulging into the stomach or duodenal lumen. Outcome measures were successful drainage of the pseudocyst, complication and recurrence rates.

Results: Sixty-six patients presented with pseudocysts of which 34 were thought to be suitable for endoscopic drainage. Twenty-four were successfully drained Failures were associated with thick-walled pseudocysts (greater than 1 cm), location in the tail of the pancreas and pseudocysts associated with acute necrotizing pancreatitis. There were no deaths and only one patient required emergency surgery for bleeding from the pseudocyst wall. There were three recurrences with a median of 41 (interquartile range 3–51) months of follow-up, two of which were successfully re-drained endoscopically. The long-term success rate of the initial procedure was 62 per cent.

Conclusion: Transmural endoscopic drainage is a safe procedure with minimal complications, although surgical facilities must be available. It should be the procedure of choice for pseudocysts associated with chronic pancreatitis or trauma, with a wall thickness of less than 1 cm and a visible bulge into the gastrointestinal lumen. Applying these criteria to the 66 consecutive patients with pancreatic pseudocysts presenting over this initial 2-year study period, 26 (39 per cent) were suitable for the procedure. Technical success was achieved in 24 of the 26 patients and long-term success in 22.

Single-centre audit of endoscopic common bile duct stone retrieval

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Background: Endoscopic extraction of stones in the bile duct is not without risk, with complications occurring in up to 10 per cent of patients. The aim of this study was to determine the success and complications of stone retrieval by endoscopic retrograde cholangiopancreatography (ERCP) in this institution.

Methods: This was a retrospective analysis of a prospective database for all ERCPs (single operator, single institution) between 1990 and 1995. Some 271 consecutive patients with a strong suspicion of bile duct stones, from history or investigations, were studied. All patients underwent ERCP and attempted retrieval of bile duct stones if detected. Treatment success was strictly defined as a stone-free postprocedure radiograph. All patients were followed to identify complications occurring within 30 days of the procedure.

Results: The median age of the 271 patients was 73 (range 17–96) years, 62 per cent were women. Some 139 patients had 162 significant other medical conditions (61 per cent cardiopulmonary) that required specialist treatment. The presenting symptoms included painful jaundice (34 per cent), acute pancreatitis (25 per cent), cholangitis (17 per cent), painless jaundice (14 per cent) and abdominal pain alone (9 per cent). Stones were seen at ERCP in 192 patients (71 per cent); the median number of stones was 1 (range 0–20). Successful endoscopic stone retrieval was achieved in 136 patients (71 per cent) at the first attempt, with an overall success rate of 90 per cent. The median number of ERCPs per patient was 1 (range 1–4). There were five false-negative ERCPs (2 per cent) and 19 retrieval failures (10 per cent), which included requirement for percutaneous cholangiography or endoscopic stenting for successful treatment. Complications occurred in eight patients (3 per cent), and included cholangitis (1 per cent), pancreatitis (less than 1 per cent) and haemorrhage (less than 1 per cent). There were two procedure-related deaths (1 per cent), from myocardial infarction and cholangitis.

Conclusion: Endoscopic stone retrieval can be achieved successfully with low morbidity and mortality rates, even in patients with significant co-morbidity These data provide further support for dedicated units offering a regional ERCP service.

Impact of endoscopic ultrasonography on the management of idiopathic pancreatitis

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Background: Conventional ultrasonography may fail to detect small stones responsible for acute pancreatitis, leading to a false diagnosis of idiopathic pancreatitis and exposing 33–66 per cent of these patients to the risk of a recurrent attack from untreated gallstone disease. The aim of this study was to assess whether identification of a potential aetiology in patients with 'idiopathic' pancreatitis, using endoscopic ultrasonography (EUS), had any effect on outcome.

Methods: EUS was performed following a diagnosis of idiopathic pancreatitis, using the GF UM-20 echoendoscope (Olympus). The presence of gallstones or other pathology was determined and any appropriate treatment was provided. The frequency of attacks of pancreatitis before and after treatment of the presumed cause was calculated.

Results: Of 20 patients with idiopathic pancreatitis, evidence of gallstone disease (e.g. stones, microlithiasis) was seen in 12 patients leading to endoscopic sphincterotomy and/or cholecystectomy in nine. Pancreatic disease was seen in three patients, of whom one underwent pancreatic duct stenting. One patient underwent cholecystectomy for recurrent pain, despite a normal EUS result, with a diagnosis of acalculous cholecystitis. No pathology was seen in a further four patients. The frequency of attacks of pancreatitis was 1 1 per patient-year before treatment *versus* 0 per patient-year after treatment ($P < 0\ 0001$). The overall morbidity rate from investigation and treatment was 0 05 per cent. This resulted from one episode of post-ERCP pancreatitis following endoscopic sphincterotomy, which resolved rapidly with conservative treatment.

Conclusion: EUS is able to detect pancreatic and biliary abnormalities that are not visible with conventional ultrasonography and can guide appropriate treatment. EUS should be performed before a diagnosis of idiopathic pancreatitis is made, to reduce the risk of recurrent pancreatitis from unrecognized gallstones or other pathology.

Lateral resection margin and prognosis following R_0 resection for oesophageal carcinoma

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Background: For patients with rectal carcinoma, the finding of tumour within 1 mm of the circumferential resection margin is of independent prognostic importance. For patients undergoing oesophageal resection the significance of finding tumour within 1 mm of the lateral margin has not been described prospectively

Methods: A series of 68 patients undergoing radical R_0 oesophagectomy for carcinoma (46 adenocarcinomas) was studied prospectively. The resection specimens were examined prospectively by one pathologist and staged using the 1987 tumour node metastasis (TNM) classification. In addition, specimens in which tumour cells were seen within 1 mm of the lateral margin were regarded as being circumferential margin (CRM) positive. Survival was calculated using the Kaplan–Meier method and the Cox hazard model was used to identify independent effects on survival.

Results: The overall 3-year survival rate was 30 per cent (56 per cent stage I, 42 per cent stage II and 19 per cent stage III, $P < 0.04$) Although for patients with the CRM involved ($n = 38$) the survival rate was 20 per cent compared with 40 per cent in those in whom tumour was more than 1 mm from the lateral margin ($P = 0.15$), using Cox's proportional hazards model the effect of CRM involvement was not independent of the TNM stage.

Conclusion: The impact of CRM involvement in oesophageal cancer may be less marked than for rectal carcinoma. A larger study is needed to quantify the true importance of CRM involvement, particularly with the increasing use of neoadjuvant therapies.

Pattern of lymph node dissemination from adenocarcinoma of the oesophagogastric junction

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Background: Adenocarcinoma of the oesophagogastric junction (OGJ) is rapidly increasing in incidence and the role of radical lymphadenectomy for such tumours remains controversial. The aim of this study was to identify the pattern of metastatic nodal spread by histopathological assessment of all lymph node groups retrieved from resected specimens.

Methods: Data were collected prospectively from patients undergoing potentially curative (R_0) resection with lymphadenectomy for adenocarcinoma of the OGJ between January 1996 and May 1998. Patients with type 1 tumours (lower third of the oesophagus) underwent two-stage subtotal oesophagogastrectomy with two-tier lymphadenectomy. Patients with type 2 (gastric cardia) tumours underwent D_2 total gastrectomy. At the time of surgery all lymph node groups were dissected out from the specimens, labelled and assessed by a single consultant histopathologist.

Results: A total of 103 patients were studied. Eleven patients were understaged before operation and were inoperable or had palliative resections. Of the remaining 92 patients, 68 had type 1 tumours and 24 had type 2 tumours. Some 2301 nodes were analysed representing a median of 27 nodes per patient (26 from the oesophagectomy group and 30 from the gastrectomy group) Over 70 per cent of all patients had lymph node metastases at the time of surgery. Some 6 per cent of type 1 tumours with lymph node metastases had dissemination in both the abdominal and mediastinal nodal tiers. The common abdominal sites were the paracardial (right, 23 of 41, left, 23 of 41) and left gastric nodes (29 of 41) whereas within the mediastinum paraoesophageal (25 of 41) and bronchial (right, seven of 41; left, six of 41) metastases were more often encountered. Type 2 tumours had positive lymph nodes most frequently in the left paracardial (nine of 16), lesser curve (11 of 16) (N_1 group) and left gastric (eight of 16) (N_2 group) territories. The extent of lymph node positivity correlated with the T stage and differentiation of the primary tumour, as well as the presence of perineural, lymphatic and vascular invasion ($P < 0.05$).

Conclusion: The high incidence and widespread dissemination of nodal metastases at the time of surgery seen with these tumours may justify the approach of systematic lymphadenectomy in the hope of performing a curative resection. The current definition of the lymph node sites in the abdominal and mediastinal tiers for type 1 tumours is based on experience with lower-third squamous carcinomas. These results demonstrate a different pattern of dissemination for junctional oesophageal adenocarcinomas requiring redefinition of the nodal stations to be resected in radical lymphadenectomies for such tumours.

Cost implications of endoscopic surveillance of patients with Barrett's oesophagus

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Background: The cost implications of a 13-year endoscopic surveillance programme for patients with Barrett's oesophagus were assessed and it was considered whether this represents a justifiable use of resources.

Methods: From a population of 597 patients with Barrett's oesophagus, 357 patients (207 men, mean age 61 years) entered a yearly endoscopic surveillance programme. Twelve patients (11 men) developed adenocarcinoma a mean of 72 months after entering the programme. The costs of the surveillance programme were calculated using figures for this institution.

Results: The cost of detecting one cancer at the institution's incidence rate of one cancer per 69 patient-years of follow-up was £24 236. The cost for male patients was £15 801 and for female patients £122 973. For male patients with specialized mucosa the cost was £13 969 per cancer detected. Comparing the stage presentation of surveillance cancers with the stage of adenocarcinomas presenting generally in this institution, the cost per life-year saved was estimated at £6097 for male patients.

Conclusion: Yearly endoscopic surveillance of patients with Barrett's oesophagus is expensive compared with other established screening programmes (e.g. £6006 per breast cancer detected) but for male patients with specialized mucosa it is probably justified. However, its role in female patients must be questioned given the high cost and low yield of cancers.

Prospective randomized trial of laparoscopic Nissen fundoplication *versus* maintenance proton pump inhibition in the treatment of gastro-oesophageal reflux disease in patients aged under 65 years: preliminary results

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Background: Laparoscopic Nissen fundoplication (LNF) was compared with maintenance proton pump inhibition (PPI) in patients with gastro-oesophageal reflux disease (GORD).

Methods: Some 113 patients (60 men; median age 45 (range 25–64) years) presented between June 1997 and June 1998 with a history of GORD of at least 2 years' duration. After giving informed consent they were investigated by endoscopy, 24-h pH and oesophageal manometry. Of 66 patients who completed the investigations, 57 had significant GORD; these were randomized, 29 to PPI and 28 to LNF.

Results: Endoscopic findings were equivalent in the two groups· 75 per cent of the PPI group had a hiatus hernia compared with 78 per cent of the LNF group; 54 per cent of the PPI group had oesophagitis compared with 71 per cent in the LNF group. Twenty-four-hour pH monitoring revealed De Meester scores of 21 (range 7–92) in the PPI group compared with 20 (range 10–99) in the LNF group. Manometry revealed a median lower oesophageal sphincter pressure (LOSP) of 10 (range 0–30) mmHg in the PPI group compared with 7 (range 1–30) mmHg in the LNF group. At 3 months after start of therapy, 24-h pH monitoring revealed a median De Meester score of 11 for both groups (PPI range 7–24, LNF range 9–39). Median LOSP was 15 mmHg in the PPI group compared with 17 mmHg in the LNF group.

Conclusion: Preliminary results suggest that LNF provides the same reduction in acid reflux as maintenance PPI in the short term. Further study of this group of patients will assess not only the physiological benefits of surgery *versus* maintenance PPI but also its impact on well being and relative costs of the two treatments.

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

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Informed consent in patients with acute abdominal pain

Letter 1

Sir

We welcome the paper by Vessey and Siriwardena (*Br J Surg* 1998; **85:** 1278–80) which highlights the important issue of informed consent in surgical practice. We are, however, concerned whether the patients received the appropriate information and who obtained consent. We recognize that it is difficult to standardize the information given for the wide range of operations encompassed by emergency abdominal surgery. The study does not confirm that the information assessed at recollection was ever given or, at least, documented as having been given. It also appears that consent was obtained by the preregistration house surgeon. We feel that this is unacceptable as the operating surgeon should be more informed regarding the risks and possible outcome of emergency surgery.

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Letter 2

Sir

We read with interest the article by Vessey and Siriwardena in which they demonstrate that the process of gaining 'informed consent' for emergency abdominal surgery was inadequate as a result of poor communication, and not preoperative pain or opiate analgesia. Although this is a novel situation in which to make the observation, it is a finding consistent with other studies.

Preregistration house officers were responsible for gaining consent for operation during the study, a practice which has been shown to be lacking[1] But is this a problem? No patient in the study expressed dissatisfaction. Warning of possible complications does not necessarily alter the patient's reaction if they subsequently occur[2].

The authors do not draw any conclusions from their study. Do they believe their practice is appropriate or has their practice changed as a consequence? What is ideal practice? In the UK the Bolam test applies to the issue of consent[3]. We currently seem to be heading towards the standardization of information given to patients which has the effect of taking responsibility away from the clinician. A committee designs suitable 'information sheets' and the responsibility to read them lies with the patient. While on the surface this appears to be good risk management, it may also provide problems of its own, particularly by confusing some patients with too much information. All patients require different information, both in quality and quantity, and the responsibility to make the individual judgement lies with the attending clinician

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1 Richardson N, Jones P, Thomas M. Should house officers obtain consent for operation and anaesthesia? *Health Trends* 1996; **28:** 56–9.
2 Thorpe AC, Cleary R, Coles J, Reynolds J, Vernon S, Neal DE. Written consent about sexual function in men undergoing transurethral prostatectomy. *BJU* 1994; 74. 479–84.
3 Sidaway *versus* Board of Governors of Bethlem Royal Hospital, 1985 AC 871.

Authors' reply

Sir

We appreciate the interest generated by our work Daniels and Loosemore highlight the fact that our study did not assess whether the information pertaining to the informed consent interview (as assessed at the recollection interview) was actually given. At the time of the study, there were detailed patient information sheets pertaining to elective surgery but none dealing with common emergency surgical procedures. We are presently evaluating the feasibility of simple patient information sheets for procedures such as appendicectomy. We agree with Daniels and Loosemore that preregistration house officers should not be asked to obtain consent.

Richardson and Jones comment that the process of gaining consent for urgent surgery was inadequate, but our study examined clinical practice in emergency abdominal surgery in a single institution (a university teaching hospital) and there is no evidence to suggest that our findings are not representative of practice in other UK hospitals. We disagree with their comment that our study makes no conclusion. We remain guarded about making strong conclusions from a small qualitative analysis but agree with their closing statement that there is a perceived need for better discussion of the indications for and the likely outcomes of urgent abdominal surgical procedures.

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Current surgical practice in screening for colorectal cancer based on family history criteria

Sir

Scholefield *et al.* (*Br J Surg* 1998; **85:** 1543–6) elegantly make the case for the development of specific multidisciplinary clinics for evaluation of those at risk for colorectal cancer by virtue of their family history. In applauding this I suggest that these clinics should also include surgeons, this would ensure that they are truly 'multidisciplinary'. The Hunter Family Cancer Service established in Newcastle, New South Wales in 1997 is an example of such a service. Since its establishment we have increased the number of families known to have familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer (HNPCC) by a factor of 5. At the same time we have been able to provide evidence-based advice with regard to screening and surveillance for the large number of individuals who do not conform to the criteria for FAP or HNPCC.

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Diagnosis and conservative management of intrathoracic leakage after oesophagectomy

Sir

Sauvanet *et al.* (*Br J Surg* 1998; **85:** 1446–9) present an honest account of the difficulties of management of this complication but several issues are raised by their paper. (1) It is unclear whether the patients in whom leaks were demonstrated underwent fibreoptic endoscopy. We believe this to be a valuable investigation allowing the size and site of the defect to be ascertained as well as the vascularity of the gastric pull-up. (2) We have experienced little morbidity with immediate postoperative feeding via a tunnelled jejunal feeding tube[1]. We believe there is much to be gained from its use especially in those in whom an anastomotic leak is diagnosed when adequate enteral nutritional intake will have been established by the time of diagnosis. (3) The author does not state which three of the five patients died apart from the fact that all three with multiple organ failure succumbed. By definition, multiple organ failure puts patients into American Society of Anesthesiologists category 4/5 and surgery in this situation has little likelihood of a successful outcome.

In our experience lesser curve staple line leaks have responded well to immediate reoperation (poster at Association of Upper Gastrointestinal Surgeons meeting, September 1998). Symptomatic intrathoracic oesophagogastric anastomotic leaks have a less favourable outcome and are best managed conservatively (apart from establishing adequate pleural drainage).

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1 Rushby E, Dehn TCB. Use of immediate postoperative tunnelled jejunal feeding and subsequent nutritional status in patients undergoing oesophagogastrectomy. *Br J Surg* 1998; **85:** 420 (Abstract).

Experience with the Mainz modification of ureterosigmoidostomy

Sir

We read with interest the article by Gerharz *et al.* (*Br J Surg* 1998; **85:** 1512–16) in which they report no anorectal complications after ureterosigmoidostomy. We performed this procedure (Mainz pouch II) in a 55-year-old man with bladder cancer. Five weeks later he developed a perianal abscess and reported that he had a boil at the anus some years previously. A high anal fistula was diagnosed and treated with a seton as fistulotomy may have caused incontinence of faeces and urine. Three and 5 months later he developed a second and third abscess and these were drained and treated with a seton. Because of recurrent anorectal sepsis a colostomy was performed and urinary flow was restored through an ileal conduit. The pouch was resected. The continuous flow of urine and faeces through the anal canal may have initiated the abscess in a pre-existing fistula. After this experience we emphasize the necessity of excluding anorectal disease before any planned urinary diversion over the anorectum.

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Vascular Disorders of the Upper Extremity. 3rd revised ed.

H. I. Machleder (ed.) 234 × 159 mm Pp 515 Illustrated 1998 Armonk, New York Futura Publishing Company US$90

This third revised edition is divided into four parts. The first describes diagnostic methods, starting with the clinical examination. This chapter is relatively short and includes diagnostic methods used in the vascular laboratory. This results in duplication as the next chapter gives an outstanding description of how non-invasive methods may be used to diagnose the various conditions affecting the circulation of the upper extremity, this chapter is systematic and based on a large personal experience. The chapter dealing with angiographic investigation includes information on how various elevation tests used in the diagnosis of thoracic outlet syndrome (TOS) may affect the arteries to the upper extremity. It would have been advantageous to receive more information about the clinical significance of these findings. Furthermore, discussion about the indications for arteriographic investigation would have been interesting. In any event, the presentation contains several arteriographic images of good quality, showing the various conditions that might affect both larger and smaller arteries to the upper extremity.

Part two deals with 'cumulative trauma disorders' and gives a lot of useful information, much of which again is duplicated. It begins with a historical review and pathological anatomy, and includes treatment for some of these conditions. However, only a few of these patients have a true vascular problem; most of them become symptomatic due to neuromuscular disorder. Two chapters describe various electrophysiological methods for investigation of syndromes that may cause pain in the arm. The text on repetitive motion disorder is useful, mainly discussing this problem in office workers and musicians. As more and more people are working with a keyboard, this is an important condition to be aware of, but most of these patients have neuromuscular disease rather than vascular problems.

The chapter on arterial compression at the thoracic outlet repeats some of the information given in the other presentations of the same topic. The exposition of venous obstruction at the thoracic outlet is excellent and systematic, giving concise information about diagnosis and treatment Also the chapter on operations for recurrent TOS is good, giving a detailed step by step description of the operative technique. The chapter on the treatment of neuropathic pain is useful. Obstruction of small arteries to the upper extremity is thoroughly described and both clinical and laboratory tests are discussed in a systematic and concise way. Again, there is overlap with the text dealing with the various systemic disorders that may give vascular manifestations in the upper extremity. The latter work is excellent and includes various diseases that the vascular surgeon should be aware of, a description of immunological tests that are used to make a precise diagnosis is worthy of note. Arterial obstruction is mentioned with various backgrounds, including atherosclerosis. The effectiveness of axilloaxillary bypass for the treatment of subclavian artery obstruction is probably controversial. In this field endovascular techniques, at least in Europe, are used to a greater extent. In my opinion balloon angioplasty, with and without stenting, should have been included as a therapeutic possibility in this context. Important issues, such as vascular trauma and emboli to the upper extremities, are mentioned only in a few pages, while the various compression syndromes encompass more than 150 pages. I feel that separate chapters on vascular trauma and arterial emboli would have been justified in a book on vascular disorders of the arm. The text dealing with angiodysplasias is useful and there is also a good description of the complications that may occur in connection with vascular access procedures. In the latter chapter ligation and bypass for peripheral steal should have been mentioned.

In conclusion, this is a book to which several distinguished American doctors have contributed good chapters that, on the whole, are well illustrated and have good references. The main objection is that there is too much overlap, which may have been avoided by better communication between the authors. There may also have been a better proportion between the different chapters according to the importance of the conditions discussed. Nevertheless, there is need for a book about the various vascular disorders affecting the upper extremity. Since the quality of each chapter is good, this volume can be recommended as a reference book for vascular and orthopaedic surgeons, internists, rheumatologists, general practitioners and others who see patients with pain or vascular problems in the upper extremity.

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Vascular Diagnosis With Ultrasound. Clinical References with Case Studies

M. Hennerici and D Neuerburg-Heusler with contributions by T. Karasch and W Rautenberg. 274 × 198 mm Pp 499 Illustrated 1998 Stuttgart Thieme US$149

This text uses an interesting format of presenting the use of ultrasonography technology by presenting normal findings followed by pathological findings and then a concluding section on sources of error and diagnostic effectiveness. The text is detailed and well referenced. The diagrams presented are excellent; however, it is unfortunate that in some of the colour illustrations of duplex scans the labelling is in German. It would be helpful in a subsequent edition if this could be altered Overall, I would certainly recommend this book to vascular surgeons, radiologists and ultrasonographers. Most departments would benefit from having a copy for reference purposes. As previously mentioned, the reference list is detailed and, in comparison to other similar texts, it has a good chapter on tumour vascularization. Finally, it has a very well presented glossary on terms related to diagnostic ultrasonography.

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Surgical Disorders of the Peripheral Nerves

R Birch, G. Bonney, C. B. Wynn Parry. 283 × 223 mm Pp 539 Illustrated 1998 Edinburgh Churchill Livingstone £95

This review sets out to be a comprehensive text on the anatomy, pathology and surgery of the peripheral nerves, including the brachial plexus. The first four chapters are essentially anatomy, microanatomy, sensory and motor pathways and reactions to injury; they are an excellent introduction to these matters. The following chapters on regeneration and clinical aspects of nerve injury are also excellent, especially the section on systemic disorders presenting as peripheral nerve lesions. Chapters 7 to 12 essentially describe the surgery of a variety of disorders of both peripheral nerve and brachial plexus, the authors list the results in chapter 12 stating that they have performed over 900 repairs of the brachial plexus, a figure that merits some respect. The volume also contains fine contributions on iatropathic injury, neoplastic disease, pain, and reconstruction and rehabilitation. Electrodiagnosis is especially well set out for the non-specialist. Finally, there is something in excess of 1900 references in the text and this says much about its comprehensiveness.

There are one or two minor matters that detract from the work, namely the repeated discussion about the Latin and Greek derivations of some of the terms; the political comment on page 50 also seems out of place in a textbook of this quality. The book certainly fills a gap in the market and the authors have undoubtedly, in my opinion, achieved what they set out to do. A copy of this work should be in the library of any department dealing with peripheral nerves and I can recommend it to any surgeon in training who is likely to have to deal with peripheral nerve injuries. Overall, an excellent product.

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Scientific Surgery

The *British Journal of Surgery* is committed to practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English language publications. A collection of all these papers will be available in the Scientific Surgery Archive which will be held on *The British Journal of Surgery* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Randomized trials

Lausen I, Jensen R, Jorgensen LN, Rasmussen MS, Lyng KM, Andersen M *et al.* Incidence and prevention of deep venous thrombosis occurring late after general surgery. a randomised controlled study of prolonged thromboprophylaxis. *Eur J Surg* 1998, **164:** 657–64.

The study included 118 evaluable patients who had major abdominal or thoracic surgery. The rate of late deep venous thrombosis was not significantly reduced by a 4-week (5·2 per cent) instead of a 1-week course of tinzaparin (10 per cent).

Wansik Y, Whang I, Suh I, Averbach A, Chang D, Sugarbaker PH. Prospective randomized trial of early postoperative intraperitoneal chemotherapy as an adjuvant to resectable gastric cancer. *Ann Surg* 1998; **228:** 347–54

Among 248 patients included, there was no overall survival advantage at 5 years in those who received intraperitoneal mitomycin C and 5-fluorouracil (38·7 *versus* 29·3 per cent in controls). Survival in patients with stage III disease was improved (49·1 *versus* 18·4 per cent in controls).

Holt PR, Atillasoy EO, Gilman J, Guss J, Moss SF, Newark H *et al.* Modulation of abnormal colonic epithelial cell proliferation and differentiation by low fat dietary foods: a randomised controlled trial. *JAMA* 1998; **280:** 1074–9

Seventy patients who had an adenomatous polyp removed were included. Subjects randomized to increased dietary intake of calcium showed reduced proliferative activity of colonic epithelial cells and restoration of normal cellular differentiation.

Valls C, Lopez E, Guma A, Gil M, Sanchez A, Andia E *et al* Helical CT *versus* CT arterial portography in the detection of hepatic metastasis of colorectal carcinoma. *AJR Am J Roentgenol* 1998, **170:** 1341–7

Twenty-one patients had both imaging methods before surgery. Helical computed tomography (CT) (sensitivity 76 per cent, positive predictive value 90 per cent) was superior to CT arterial portography (74 and 69 per cent respectively).

Hawkey CJ, Tulassay Z, Szczepanski L, van Rensburg, Filipowicz-Sosnowska A, Lanas A *et al* Randomised controlled trial of *Helicobacter pylori* eradication in patients on non steroidal anti-inflammatory drugs; HELP NSAIDs Study. *Lancet* 1998; **352:** 1016–21.

Eradication therapy actually reduced the healing rate of gastric ulcers but did not affect duodenal ulcers in the 285 patients randomized. The rates of recurrent ulceration and dyspepsia were similar.

Pietra N, Sarli L, Costi R, Ouchemi C, Grattarola M, Peracchia A. Role of follow-up in management of local recurrences of colorectal cancer – a prospective randomized study *Dis Colon Rectum* 1998; **41:** 1127–33.

Some 207 patients were randomly assigned routine or intense follow-up. The 5-year survival rate was better in patients who had intense follow-up (73·1 *versus* 58·3 per cent, $P < 0·02$).

Bold RJ, Mansfield PF, Berger DH, Pollock RE, Singletary SE, Ames FC *et al.* Prospective, randomized, double blind study of prophylactic antibiotics in axillary lymph node dissection. *Am J Surg* 1998; **176:** 239–43.

Two hundred patients were included, half received a perioperative infusion of cefonicid (second generation cephalosporin). Infection rates were not significantly different (6 per cent antibiotic *versus* 13 per cent placebo), but fewer patients required admission for infection after prophylaxis was used.

O'Riordain DS, Kelly P, Horgan PG, Keane FBV, Tanner WA. A randomized controlled trial of extraperitoneal bupivacaine analgesia in laparoscopic hernia repair *Am J Surg* 1998, **176:** 254–7.

Local anaesthetic instillation improved postoperative pain scores, reduced analgesia requirement and speeded return to full activity (2·5 *versus* 5 days, $P = 0·013$) in this study of 56 operations.

Cuniffe MG, McAnena OJ, Dar MA, Calleary J, Flynn N. A prospective randomized trial of intraoperative bupivacaine irrigation for the management of shoulder tip pain following laparoscopy. *Am J Surg* 1998, **176:** 258–61.

A total of 105 patients undergoing a variety of laparoscopic procedures were included. Shoulder tip pain was reduced from 42 to 7 per cent after local anaesthetic irrigation ($P = 0·003$).

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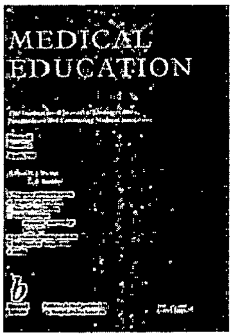

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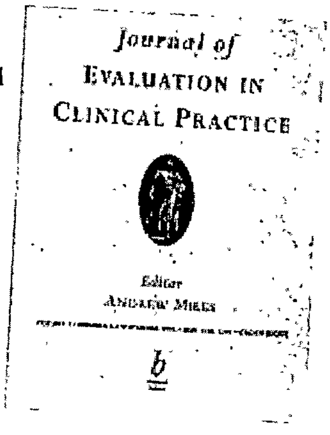

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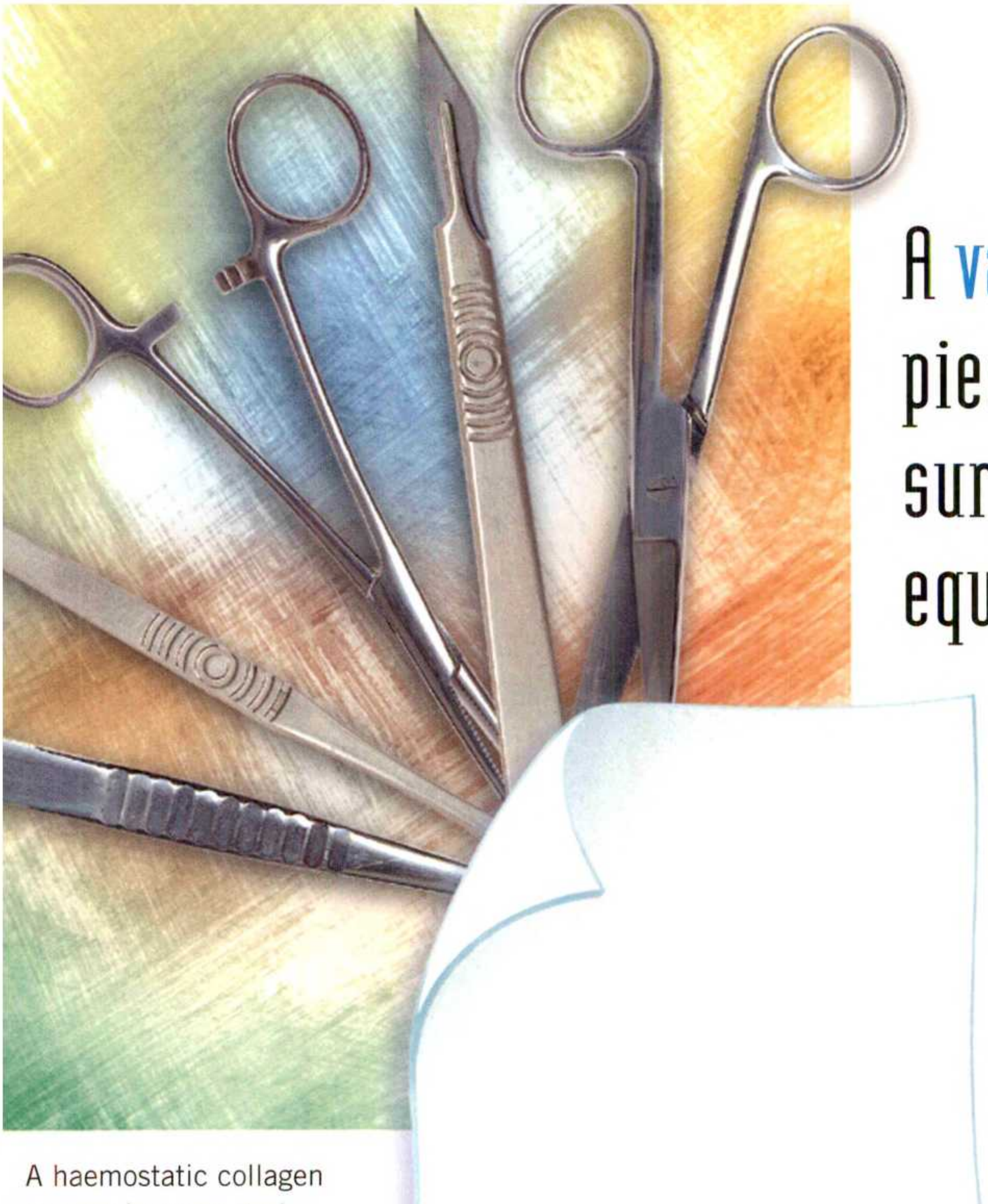

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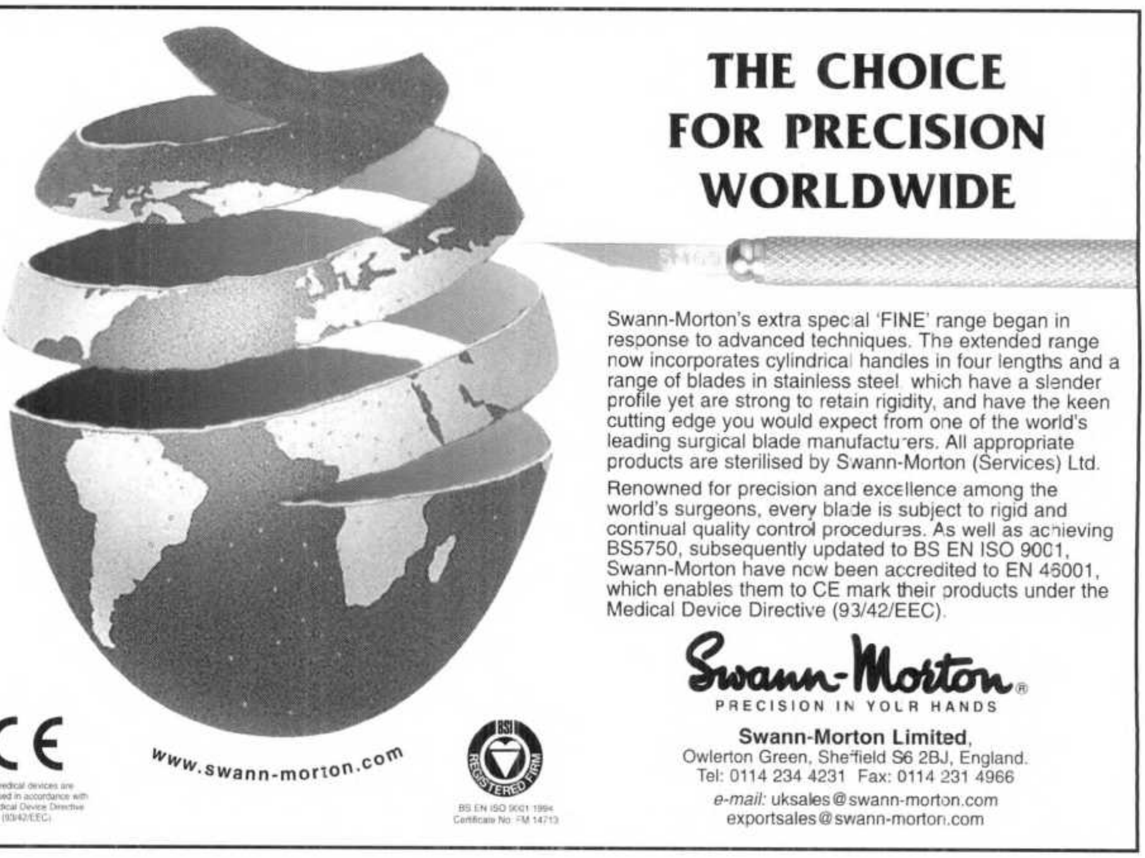

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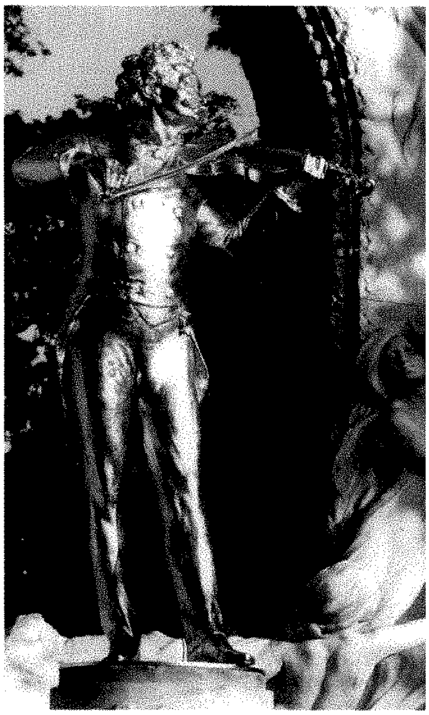

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Management of small abdominal aortic aneurysms

D. Bergqvist

Department of Surgery, University Hospital, S-751 85 Uppsala, Sweden

Before the era of computed tomography and ultrasonography the management of abdominal aortic aneurysm (AAA) was fairly simple. Those detected were often large and the natural course was malignant with a high rupture rate within a few years. With decreasing perioperative and postoperative mortality rates, the indications for operative intervention were widened and smaller aneurysms were accepted for open surgical treatment, the results of which are durable in a long-term perspective. As the great threat with an AAA is rupture, with an overall case fatality rate of the order of 80–90 per cent[1,2], superficially it would seem reasonable and tempting to screen for small AAAs and operate prophylactically. This would be logical were it not for the fact that only about 15 per cent of all AAAs rupture; the remaining 85 per cent of patients die from causes unrelated to aneurysm[1]. So early surgery of the many would induce a risk of postoperative death and morbidity in patients whose AAA would never cause any problem. Another suggested option is to use the 'simple' endoluminal repair. With such a new technological modality there is a threat of widening the indications in two directions – to treat more patients with smaller aneurysms earlier in life and to treat so called 'compassionate' cases, for which open surgery is considered to be contraindicated. With these general comments there are several contemporary issues relating to small AAAs which merit consideration.

(1) Not all authors define an aneurysm in the same way, but the definition of the Ad Hoc Committee on Reporting Standards seems reasonable – a permanent localized aortic dilatation having at least 50 per cent increase in diameter compared with the expected normal diameter[3]. Not all authors agree on what a small AAA is, but below 5 cm in diameter the risk of rupture seems minimal[4]. The UK Small Aneurysm Trial[5] published very recently used a diameter between 4 and 5·5 cm.

(2) A critical point concerns the natural history of small AAAs. The expansion rate is exponential; those less than 5 cm expand by 0·17–0·57 mm a year although there are substantial variations because of non-comparability between studies[6]. The rupture rate is very small but there is a decreased survival because of concomitant cardiovascular diseases[7,8].

(3) The question of whether or not screening is worthwhile is controversial; the final answer would need a large trial in which populations were randomized to screening or not and at follow-up analysed with respect to survival.

(4) From a patient's point of view it is important to know the influence of a small AAA once detected. If an invasive treatment is not chosen, how should the patient be informed? Should the AAA be followed by repeat ultrasonography and how would such a situation influence quality of life?

(5) What is the optimal surveillance interval when following aneurysm expansion to choose those who need invasive treatment in the future?

(6) Has the situation changed with the introduction of endovascular methodology in the treatment of AAA? Initial optimism seems to have changed in the light of the various complications now reported from long-term follow-up data; this is not very surprising. Without doubt, however, endovascular treatment will find a place in the future.

(7) Are there clinical situations in which small AAAs still should be operated? For instance, how should one treat a 45-year-old man in whom ultrasonography has detected a 4·5-cm AAA, the investigation being motivated by the knowledge that the patient's father died at 62 years of age from a ruptured AAA and that an older brother was operated on recently at a nearby hospital because of a 5·5-cm AAA? The genetic component is clear and one knows that the aneurysm will expand (although in the individual patient one does not know how rapidly). The patient will also become older and probably accrue added risk factors for surgery.

So there are several important questions about small AAAs, but at least our knowledge has increased by the publication of the UK Small Aneurysm Trial[5]. In this study 1090 patients, aged between 60 and 76 years with an asymptomatic AAA of 4·0–5·5 cm in diameter, were randomized to early elective open repair or to ultrasonographic surveillance and surgery if certain predefined criteria became fulfilled. As might be expected, the 30-day mortality rate of 5·8 per cent in the open repair group resulted in an early disadvantage for this arm of the study, but at 2, 4 and 6 years of follow-up there was no difference in mortality rate between the groups. It could be agreed that the results do not support a policy of open surgical repair for AAAs of 4·0–5·5 cm in diameter. Our British colleagues are to be congratulated on having performed this important study, which stands out as a classic among the many publications on AAA, most of which do not fulfil even the most basic of methodological criteria. The main conclusion of the trial seems irrefutable – survival is not influenced by early surgical intervention.

I have two principal concerns. The first is the upper size limit of 5·5 cm. One is still left with some uncertainty about AAAs of 5–5·5 cm, for which there seems to be an advantage (although not statistically significant) in favour of surgery; others have suggested 5 cm as a critical limit in practical patient care. The other problem which is difficult to solve, and which is not specific to this study, is the low autopsy rate. Obviously total mortality is a robust outcome measure and the most important one from a patient's point of view; however, one cannot help but be curious about the specific causes of death. In a study such as the UK Small Aneurysm Trial it seems probable that the knowledge that a patient has an AAA would lead to bias in favour of that disease being considered the cause of death in many unclear circumstances where there is no autopsy. Two final comments seem possible. An important extrapolation of the UK study is that, in the light of present results of endovascular aneurysm repair, there is little reason to widen the indications for this technique in small aneurysms just because they are simpler to deal with from a technical point of view. Also, the prevalence of small AAAs as defined in the UK study seems to be around 4 per cent[9]; there is certainly no indication to screen for these.

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Aortic prosthetic infection

A patient has suspected infection of an aortic prosthesis. What should be the operative strategy, particularly in the era of methicillin-resistant Staphylococcus aureus? *In the light of his experience in Leicester, Mr Ross Naylor replies.*

The first dilemma when faced with suspected aortic graft infection is whether immediate surgery is required. While unavoidable in patients with profuse gastrointestinal haemorrhage and suspected aortoenteric fistula, immediate operation incurs the disadvantage of lack of complete preoperative assessment. In less acute cases, the investigative protocol at Leicester Royal Infirmary includes contrast-enhanced computed tomography (CT) (air–fluid interface, gas bubbles, false aneurysm or abscess formation), angiography (vascular anatomy) and CT-guided aspiration (organism and sensitivities). Isotope-labelled white cell scans are reserved for situations in which the CT findings are equivocal. Thereafter, the principles that guide operative planning reflect the complex balance between the eradication of infection and the avoidance of unnecessary morbidity and mortality. While the 'gold standard' remains total graft excision and revascularization, less radical options (partial excision, obturator bypass, antibiotic irrigation, anastomotic wrapping with gentamicin sponge) are occasionally appropriate for the high-risk patient.

Total graft excision is a difficult operation which should be performed only in experienced vascular units. From a practical viewpoint, severe haemorrhage from an aortoenteric fistula can be controlled by inserting a balloon catheter via the femoral artery to occlude the aorta at the level of the proximal false aneurysm[1]. This enables the anaesthetist to stabilize the patient, thereby reducing the urgency and danger of dissection through adhesions and the inevitable inflammatory mass. The next priority is control of the aorta at the diaphragm; no attempt is made at this point to control this vessel by direct dissection through the inevitable retroperitoneal inflammatory mass. Once proximal control has been achieved, it is usually possible to expose a segment of relatively normal juxtarenal aorta and adjacent inferior vena cava by reflecting the right colon, duodenum and head of pancreas medially. This useful approach, popularized by transplant surgeons, often goes unmentioned in operative texts on revisional surgery of the aorta. If necessary the left renal vein may be divided under clear vision, but this should be avoided when possible. The suprarenal aorta is similarly exposed via medial visceral rotation of the left colon, spleen and pancreas. Only when the aorta and distal anastomoses have been controlled is the anterior inflammatory mass opened. Any bowel defects are repaired or resected. The vascular prosthesis is removed entirely and the proximal aortic wall trimmed back to leave healthy tissue for closure or reconstruction. The prosthetic bed is then carefully debrided, the tunnel tracks irrigated with aqueous povidone–iodine, and specimens of prosthesis, anastomosis and tissue sent for culture.

Options for revascularization are the subject of endless debate; they are unlikely to be subjected to randomized comparison. It seems probable that each has a role in different situations. The main options include extra-anatomic bypass, or *in situ* revascularization with an antibiotic-bonded prosthesis or transposed superficial femoral vein. The standard extra-anatomic approach involves (bi)axillo(bi)femoral–popliteal bypass followed by total prosthetic excision and oversewing of the aortic stump. Potential problems include obtaining sufficient debrided (uninfected) aorta to permit safe stump closure such as to prevent secondary haemorrhage, which is usually fatal, and avoiding renal failure following thrombosis of the aortic stump. Gluteal ischaemia is a risk, as is amputation as a result of the inferior patency of extra-anatomic bypass. *In situ* replacement has the advantage of enhanced flow and superior patency, while the proximal aorta can be debrided to the level of the renal arteries if necessary. However, although initial experience has been encouraging[2], long-term data suggest that the *in situ* technique is probably unwise in the presence of methicillin-resistant *Staphylococcus aureus* (MRSA)[3].

In the current era of MRSA, surgeons still have little evidence on which to base management. However, a 10-year audit of outcome following treatment of aortic graft infection has allowed the vascular unit at this hospital to devise a strategy. Eleven of 13 patients died or required major limb amputation following total graft excision and extra-anatomic bypass; these depressing results were the catalyst for considering the *in situ* technique proposed by Strachan *et al.*[4]. Experience with *in situ* replacement in 11 patients, although encouraging with a 30-day mortality rate of 18 per cent, an amputation rate of zero and a late reinfection rate of 15 per cent, indicated a poor outcome in patients with MRSA infection[3]. As a consequence, *in situ* revascularization using transposed superficial femoral vein[5] was considered to be potentially safer than an antibiotic-bonded prosthesis in those suspected of having MRSA. However, this has now been revised following the presentation of two patients with infrainguinal arterial reconstructions using autologous vein who suffered life-threatening haemorrhage as a direct consequence of deep MRSA infection. Clearly, autogenous tissue is no deterrent or barrier to MRSA.

In the light of the above, if a patient were now to present within 3 months of the original procedure with a suspected aortic prosthetic infection (i.e. probably due to a virulent organism) or if a positive preoperative MRSA culture were obtained, the preferred option would be extra-anatomic bypass followed immediately by total graft excision. Although the long-term patency of such a bypass is inferior and there is a potential risk of fatal aortic stump blowout due to ongoing infection, it seems unwise to place a further prosthesis or autogenous vein within tissues that are heavily contaminated with such a virulent organism. If, however, the nature and sensitivities of less pathogenic organisms were known before operation, or if the infection occurred late, the procedure of choice would remain *in situ* replacement with a rifampicin-bonded prosthesis. This is particularly the case if the original aortic procedure was for occlusive as opposed to aneurysmal disease so as to preserve the gluteal circulation.

Where the infective process involves the suprarenal aorta, in-line or *in situ* revascularization is unavoidable. In this rare but difficult situation a rifampicin-bonded prosthesis can originate from the supracoeliac or thoracic aorta with distal outflow via the obturator foramina. Visceral arteries may be reimplanted while organ perfusion is maintained via shunts whose inflow is derived from a temporary conduit anastomosed to the axillary artery[6]. One deletion to the protocol has been the abandoning of adjuvant retroperitoneal antibiotic irrigation. Although good results have been reported with this method[7], this unit has had major problems with candidiasis, with one fatality[3].

After operation, patients are maintained on systemic antibiotics for 2 weeks, usually a cephalosporin and metronidazole, or until sensitivities are available. Appropriate oral antibiotics are then continued for 6 weeks or until there is no clinical evidence of ongoing infection. Intravenous vancomycin or teicoplanin is used if there is any suspicion of MRSA. If MRSA is subsequently confirmed, the patient receives intravenous vancomycin or teicoplanin via a tunnelled Hickman line for 6 weeks. Experience has also shown that MRSA induces a profound and persisting anorexia; enteral feeding via a percutaneous gastrostomy should be started from the outset.

With the increasing spread of MRSA, vascular surgeons and their patients face an uncertain outlook, particularly as vancomycin- and teicoplanin-resistant strains are emerging[8]. The development of robust management strategies will require vascular units to pool their resources and experience. To this end the UK Joint Vascular Research Group is currently auditing the outcome of all graft infections and a national multidisciplinary working party is reviewing all aspects of care. This should provide valuable guidance for the future.

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Endoscopic band ligation of oesophageal varices

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Background: For 25 years the optimal management of bleeding oesophageal varices has included endoscopic injection sclerotherapy (EIS) both to arrest bleeding and to prevent rebleeding. However, the recent innovation of endoscopic variceal ligation (EVL) may be a more effective treatment; this paper reviews its efficacy.
Methods: All Medline (National Library of Medicine, Washington DC, USA) articles containing the text words 'oesophageal varices', 'sclerotherapy' or 'band ligation' were reviewed. Prospective randomized studies comparing sclerotherapy with band ligation, or combinations thereof, were included.
Results: After an acute variceal bleed EVL is as effective as EIS for control and eradication of oesophageal varices. Initial control of bleeding is similar, but eradication is achieved in fewer sessions with EVL. EVL is associated with lower rebleeding rates and fewer procedure-related complications; it is also more effective for control of active bleeding at initial endoscopy. Combination therapy (EIS plus EVL) confers no advantage over EVL alone.
Conclusion: EVL is similar to EIS for control of bleeding varices, but the former has less associated morbidity, lower rebleeding rates and achieves more rapid variceal eradication. EVL should be considered the endoscopic treatment of choice in the management of variceal haemorrhage.

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Introduction

Bleeding from oesophageal varices is the major complication of portal hypertension and occurs in up to 30 per cent of patients with chronic liver disease. The mortality rate associated with the initial bleed is 30–50 per cent and that of subsequent bleeds is 30 per cent[1,2]. Endoscopic techniques are the optimal first-line treatment for acutely bleeding varices, either alone or in combination with pharmacological agents to reduce splanchnic blood flow and lower portal pressure. Such techniques are also optimal for subsequent long-term management to prevent rebleeding[3–8]. When they fail, the percutaneous insertion of a transjugular intrahepatic portasystemic shunt usually achieves a rapid reduction in portal venous pressure with control of bleeding. As a result, urgent surgical procedures such as the creation of a portasystemic shunt or oesophageal transection are now seldom performed for acute variceal haemorrhage.

Endoscopic treatment was first used in 1936, when quinineuretan was injected into the bleeding varices of a 19-year-old woman[9]. However, endoscopic injection sclerotherapy (EIS) was largely ignored until the 1970s when Johnston and Rodgers[10] described successful control of acute variceal bleeding with injection sclerotherapy in 93 per cent of 115 patients, with an associated mortality rate of only 18 per cent. Further studies in the late 1970s and 1980s established EIS as a viable alternative to surgery[5,11], and several randomized controlled trials confirmed its efficacy[11–16]. The risk of further bleeding is reduced by variceal obliteration with repeated sclerotherapy, and some studies demonstrated an improved overall survival[10,12].

Although EIS provides effective treatment, there is potential for improvement as sclerotherapy is associated with (1) variceal rebleeding in 20–50 per cent of patients[17–22] and (2) a high rate of local and systemic complications[17,23–26]. A major disadvantage of EIS is oesophageal injury from inadvertent extravariceal leakage of sclerosant at the injection site which may lead to ulceration, bleeding, perforation or stricture formation in a substantial proportion of patients[17,23–26]. Because of such limitations, endoscopic variceal ligation (EVL) was developed as an alternative. The objectives of variceal band ligation are to provide an endoscopic treatment as effective as injection sclerotherapy but with the advantages of (1) technical ease, (2) quicker variceal eradication, (3) fewer episodes of rebleeding and (4) safety, with fewer local and systemic complications[27–30]. This article evaluates the current status of EVL by a review of published prospective randomized studies comparing EVL with EIS.

Techniques of endoscopic variceal ligation

Standard technique: single-shot band application

An ingenious device attached to the tip of a flexible endoscope is used to ensnare an oesophageal varix with a rubber band in a similar fashion to banding internal haemorrhoids. The endoscopic variceal banding device (C. R. Bard, Tewksberry, Massachusetts, USA) consists of an outer housing cylinder, an inner banding cylinder, a trip wire and an elastic *O* ring (*Fig. 1*). The outer housing cylinder attaches to the end of the endoscope by means of a silastic friction mount (*Fig. 2*). The banding cylinder is a smaller cylinder fitted with an inner clasp that allows attachment of the trip wire. The banding cylinder is constructed to fit snugly, yet slide smoothly, inside the housing cylinder. The monofilament trip wire has a flange at the distal end which attaches to the banding cylinder. The small elastic *O* ring is stretched and mounted on the banding cylinder (*Fig. 1*).

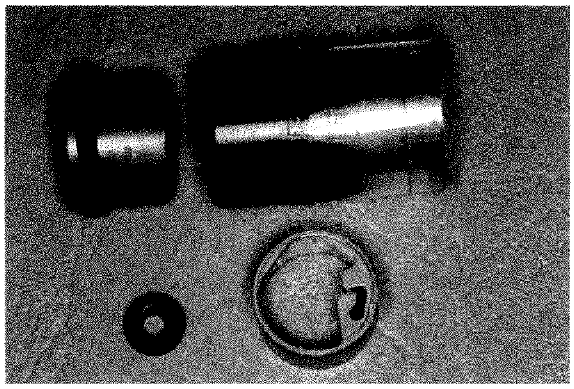

Fig. 1 Single-shot endoscopic banding device. The inner banding cylinder is illustrated with an *O* ring loaded ready for application; an unstretched band is also shown for comparison

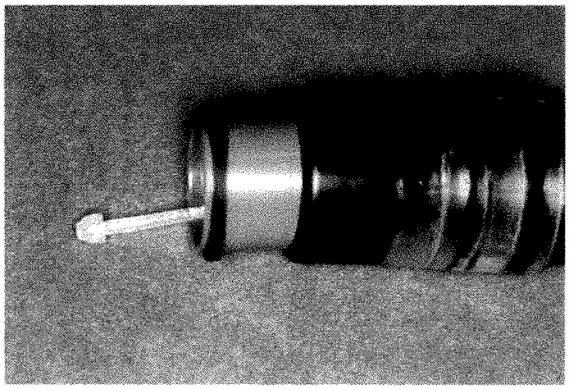

Fig. 2 Single-shot banding device mounted on to the tip of a standard endoscope. The trip wire is illustrated protruding from the tip

After completing the diagnostic panendoscopy, confirming variceal bleeding and the need for banding, the endoscope is removed and the banding device is assembled by securing the housing cylinder to the end of the scope. The trip wire is passed through the vacuum lock of the biopsy channel entry port and exits through the biopsy channel opening at the tip of the scope. The trip wire is secured to the clasp in the banding cylinder, and the banding cylinder is loaded into the housing cylinder. The banding cylinder is positioned such that approximately 1 mm of the cylinder protrudes beyond the *O* ring, which is seated against the end of the housing cylinder (*Fig. 2*).

Unlike injection sclerotherapy, the technique of EVL is standardized. The endoscope is passed through a plastic overtube and the endoscope–overtube combination is inserted into the oesophagus. The target varix is identified and the scope is advanced under direct vision until the banding cylinder is in full 360° contact with the varix (*Fig. 3a*). After full contact is made, suction is applied by depressing the endoscopic aspiration control valve, which draws the varix and surrounding mucosa into the banding chamber (*Fig. 3b*). Once the chamber is completely filled by the varix, which is evident by a complete 'red-out' and loss of endoscopic visibility, the trip wire is pulled (*Fig. 3c*) to pull the inner cylinder deeper into the outer cylinder which pushes off the elastic band over the varix. The engorged varix is strangulated at the mucosal junction (*Fig. 3d*). The endoscope is removed and the inner cylinder reloaded with a fresh *O* ring for further variceal banding[27–29].

Treatment begins with ligation of the most distal variceal columns in the oesophagus just above the gastro-oesophageal junction, commencing with the bleeding varix, if one is present. Subsequent ligations of the remaining varices are performed at increasingly higher levels, proceeding upward in a spiral fashion to avoid circumferential placement of bands at the same level. Large varices should have additional bands placed more proximally within the distal 10 cm of the oesophagus, and all visible variceal channels should be ligated at least once at each banding session. A 2-cm mucosal bridge between adjacent bands is essential to minimize mucosal necrosis, rebleeding and dysphagia. After banding, patients eat soft food for 2 days. Repeated treatments are performed at intervals of 1 or 2 weeks on an outpatient basis. On

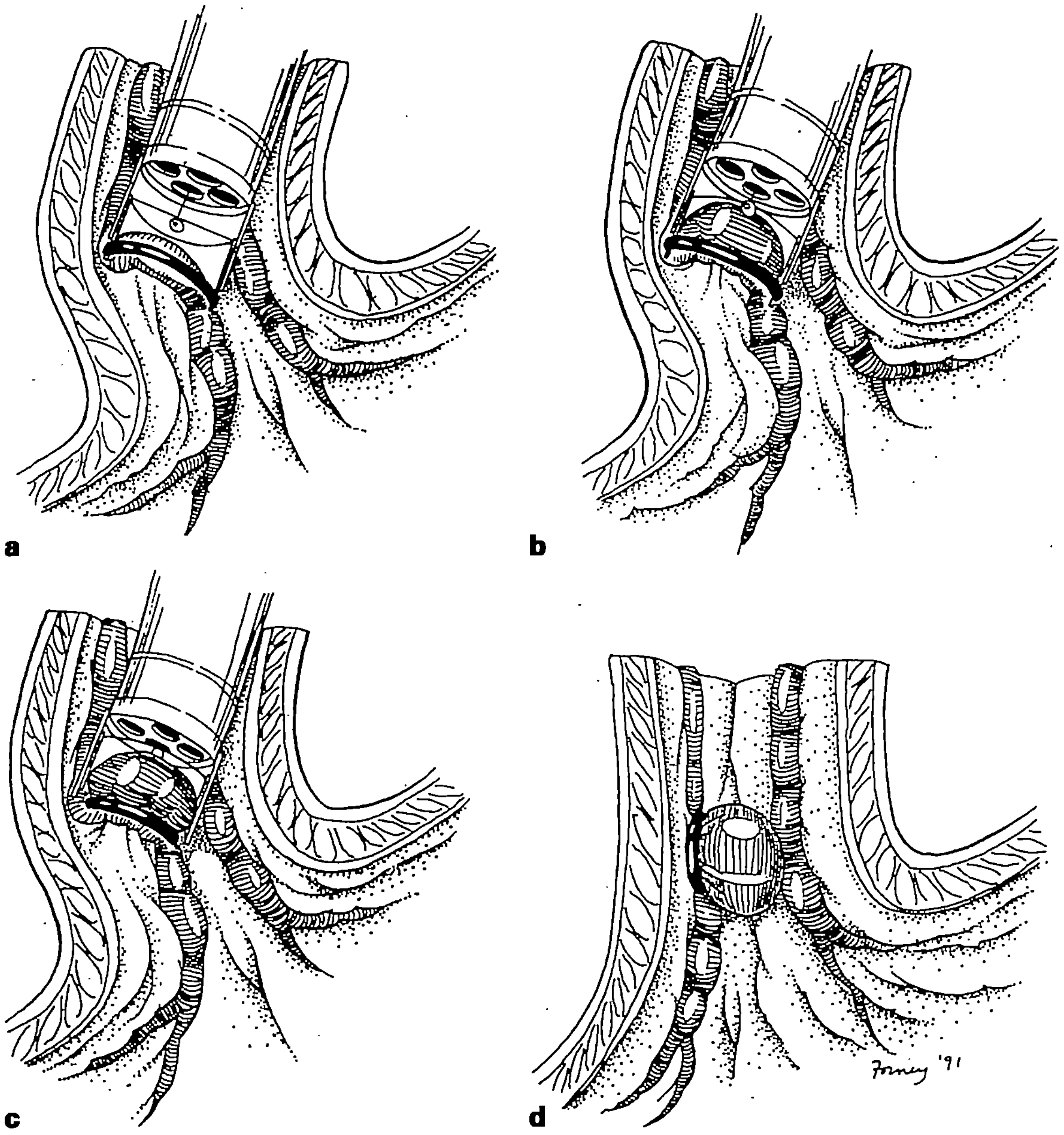

Fig. 3 Endoscopic ligation of oesophageal varices using the flexible endoscope. **a** A varix is approached under direct vision by the endoscopist. Full contact is made between the end of the ligating device and the tissue to be ligated. **b** The endoscopist activates the endoscopic suction, which results in aspiration of oesophageal mucosa, submucosa and the varix into the ligating device. **c** The trip wire (which runs through the biopsy channel of the endoscope) is pulled, which moves the inner cylinder (over which the elastic *O* ring is stretched) toward the endoscope, displacing the small elastic band. **d** The elastic band encircles the varix, resulting in strangulation and thrombosis. (Reproduced with permission from Springer-Verlag. Stiegmann GV, Yamamoto M. Approaches to the endoscopic treatment of esophageal varices. *World J Surg* 1992; **16:** 1034–41)

average six to nine bands are applied at the initial session and progressively fewer at subsequent sessions[27].

A major limitation of this (the original) technique is that only a single band can be applied per firing; the scope must be removed to reload a new band after each variceal ligation. The necessary repeated oesophageal intubation with the scope is facilitated by the flexible plastic overtube which is passed through the oropharynx into the upper oesophagus. The overtube is back-loaded on to the endoscope and, once the scope has been passed into the stomach, it is advanced over the scope by gentle rotation through the oropharynx into the upper oesophagus to minimize trauma to these structures. However, overtube insertion combined with repeated reintroduction of the endoscope can injure the oesophagus and is a principal disadvantage of this technique of EVL[31,32].

In Stiegmann and Goff's first reported clinical series[27] of 14 patients no patient was actively bleeding at the time of initial band ligation. However, two of 14 patients rebled after EVL and were subsequently controlled with emergency EVL. Varices were eradicated in ten of 14 patients, and required between one and six (mean 3·1) endoscopic sessions. Five patients had short-term dysphagia which resolved within 24 h; there were no other treatment-induced complications. Neither of the two deaths in the series was due to uncontrolled bleeding. It was this preliminary report that initiated the detailed evaluation of EVL in several prospective randomized controlled trials.

Multishot band application

Several refinements in equipment have occurred since the introduction of the original single-shot Stiegmann–Goff ligation device. The original opaque outer cylinder at the tip of the endoscope reduced visibility substantially. Replacement by a transparent outer cylinder has improved the view and 'targeting' of varices. A further innovative development has been the multiband ligator capable of carrying up to ten bands which are individually activated by a drawstring passing through the biopsy channel. This drawstring is attached to a trigger unit mounted on the biopsy port of the endoscope which is used to control the repeat firing of bands (*Fig. 4*). While the multishot system obviates the need for an overtube, it limits access to the biopsy port of the scope and requires a special adaptor for irrigation during active bleeding.

The first clinical report[33] of the multishot device described 100 per cent control of acute bleeding in five patients, and variceal eradication in 19 of 26 patients in a mean(s.d.) of 3·2(1·2) sessions. However, three of 26 patients had rebleeding, two from varices and one from treatment-induced ulceration. One patient developed an oesophageal stricture which required dilatation. While the multishot variceal band ligator can be considered as a significant technical advance over the single-shot device, its current retail cost of US $200 per unit may limit its widespread use[18].

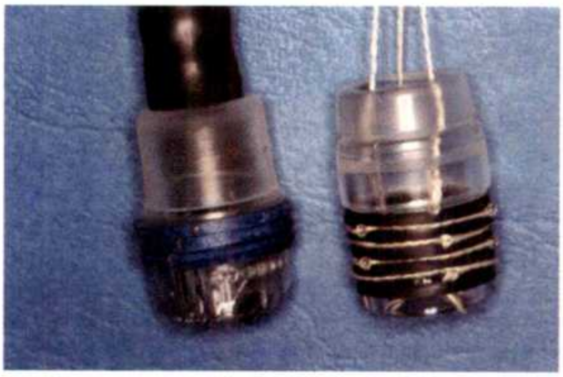

Fig. 4 Mounted and unmounted multishot banding device

Efficacy of endoscopic variceal ligation in variceal haemorrhage

While the above preliminary uncontrolled clinical reports of EVL introduced an additional treatment option for the initial management of bleeding oesophageal varices, EIS remained firmly established as the standard method of control of acute bleeding and of preventing rebleeding by variceal eradication[11,14,15]. Acceptance of EVL as an effective, safer and better technique than EIS required clear objective evidence from prospective randomized trials comparing these two techniques directly.

Endoscopic variceal ligation and endoscopic injection sclerotherapy after index variceal bleed

Seven prospective studies have been completed. The first, reported by Stiegmann *et al.*[19] in 1992, randomized 65 patients to EIS with 3 per cent sodium tetradecyl sulphate and 64 patients to EVL (*Table 1*). All were treated endoscopically within 24 h of admission. Control of acute bleeding was similar in the two groups: ten of 13 patients in the EIS group and 12 of 14 in EVL group. There was no statistically significant difference in the rates of early variceal rebleeding (48 and 36 per cent respectively) or treatment-induced bleeding (5 and 8 per cent). Eradication rates were 56 per cent with EIS and 55 per cent with EVL, with a similar mean(s.d.) number of treatment sessions required to achieve eradication, 5(2) and 4(2) respectively ($P = 0·056$). Survival was marginally better in patients with Child grade A and B disease in the EVL group ($P = 0·046$), but there was no significant difference in survival in patients classified as Child grade C. However, treatment-related complications were significantly less with EVL at 2 per cent, compared with 22 per cent for EIS ($P < 0·001$). EIS-related complications included oesophageal stricture in 12 per cent, bacterial peritonitis in 5 per cent and pneumonia in 6 per cent. The authors suggested that EVL was as effective as EIS in the management of variceal bleeding and that the former was considerably safer.

A second study[20] in 1993 randomized 39 patients to EIS and 38 to EVL. Control of active bleeding was achieved in

Table 1 Randomized trials comparing endoscopic sclerotherapy with band ligation

Reference	Year	No of patients	Treatment	No. of sessions*	Rebleed (%)	Variceal rebleeding (%)	Complications (%)	Recurrence (%)	Eradication (%)	Survival (%)
Stiegmann *et al.*[19]	1992	65	EIS	5(2)	48	52	22†	50	56	55
		64	EVL	4(2)	36	48	2	33	55	72
Laine *et al.*[20]	1993	39	EIS	6·2(0·4)†	44	31	56†	n.a.	69	85
		38	EVL	4·1(0·3)	26	24	24	n.a.	59	89
Gimson *et al.*[21]	1993	49	EIS	4·9(3·5)†	53†	51†	57	n.a.	71	37
		54	EVL	3·4(2·2)	30	24	67	n.a.	82	52
Lo *et al.*[22]	1995	59	EIS	6·5(1·2)†	51†	36†	19†	n.a	63	68†
		61	EVL	3·8(0·4)	33	11	3	n.a.	74	84
Hou *et al.*[34]	1995	67	EIS	4·6(1·6)†	33†	43	22†	30†	79	84
		67	EVL	3·5(1·6)	18	38	5	48	87	79
Sarin *et al.*[35]	1997	48	EIS	5·2(1·8)†	21	n.a.	50†	8†	92	94
		47	EVL	4·1(1·2)	6	n.a	45	29	96	94
Baroncini *et al.*[36]	1997	54	EIS	4·0(0·1)†	19	30	31†	13†	92	78
		57	EVL	3·5(0·1)	16	22	11	30	93	79

*Values are mean(s.d.). EIS, endoscopic injection sclerotherapy, EVL, endoscopic variceal ligation; n.a., data not available. †$P < 0{\cdot}05$ *versus* EVL

eight of nine patients in both treatment arms. The rebleeding rates (44 and 26 per cent respectively) and variceal eradication rates (69 and 59 per cent respectively) were similar for EIS and EVL. However, variceal eradication was achieved in fewer sessions with EVL (mean(s.d.) 4·1(0·3) *versus* 6·2(0·4); $P < 0{\cdot}001$) and was associated with fewer complications overall (24 *versus* 56 per cent; $P < 0{\cdot}01$). The incidence of infective complications and overall survival was similar in both groups. This study supported the conclusions of the Stiegmann trial, demonstrating that EVL was as effective as EIS but with fewer early complications.

A British study[21] the same year randomized 49 patients to EIS with ethanolamine and 54 patients to EVL. The importance of this study was that many more patients were actively bleeding at the index endoscopy: 21 of 54 patients treated by EVL and 23 of 49 treated by EIS. Control of acute bleeding was achieved in 19 of 21 and 21 of 23 patients respectively, but rebleeding was significantly less in the banding group (30 *versus* 53 per cent; $P < 0{\cdot}05$). In patients who survived longer than 30 days, variceal eradication was achieved in 82 per cent with EVL and 71 per cent with EIS. Eradication was achieved significantly more rapidly with banding (mean(s.d.) 39(4) *versus* 72(7) days; $P < 0{\cdot}004$) and in fewer endoscopic sessions (3·4(2·2) *versus* 4·9(3·5); $P < 0{\cdot}006$). However, survival was similar in the two treatment groups for which the Child–Pugh score was the only independent predictor of survival. In contrast to the previous two studies, the number and types of treatment-related complications were similar in both treatment arms. While this study noted a significant reduction in the rebleeding rate after EVL, this was not reflected in an improved patient survival.

A reduction in rebleeding rate after EVL was also reported by Lo *et al.*[22], who noted gastrointestinal rebleeding in 20 (33 per cent) of 61 patients treated by EVL compared with 30 (51 per cent) of 59 patients treated by EIS ($P < 0{\cdot}05$). Furthermore, site-specific variceal rebleeding was significantly lower in the banding group (11 *versus* 36 per cent; $P < 0{\cdot}01$). This study confirmed the observations of Stiegmann *et al.*[19] and Laine *et al.*[20] that banding is associated with fewer early complications. However, of greater importance was the significant improvement in overall survival reported for patients treated by EVL (84 *versus* 68 per cent; $P < 0{\cdot}02$), particularly as 30 (49 per cent) of 61 patients in the EVL group were Child grade C at the index endoscopy.

Such a survival benefit was not reproduced in the study by Hou *et al.*[34], even though patients in the EVL treatment arm had similar Child grades to those reported by Lo *et al.*[22]. In this study eradication rates were similar (79 per cent for EIS and 87 per cent for EVL) and were achieved over similar periods of time, although fewer endoscopic sessions were required to achieve eradication with banding (mean(s.d.) 3·5(1·6) *versus* 4·6(1·6)). Again, the rebleeding rate was significantly greater in patients treated by EIS (odds ratio 2·33 (95 per cent confidence interval (c.i.) 1·06–5·10)), suggesting that a reduction in rebleeding is an advantage of EVL. However, this study also reported a trend toward a higher variceal recurrence rate after EVL (48 *versus* 30 per cent; $P = 0{\cdot}08$) which may confer an increased risk of rebleeding with longer follow-up[34].

An increase in variceal recurrence rate after EVL was corroborated in two prospective randomized studies published in 1997[35,36]. Sarin *et al.*[35] reported similar eradication rates in fewer sessions with EVL, and a reduced risk of rebleeding after ligation (6 *versus* 21 per cent; $P < 0{\cdot}05$) although this did not influence patient survival. Many patients were Child grade A in this study which is reflected in the high survival rates for both treatment arms and permits long-term follow-up. Significantly more variceal recurrences occurred after EVL (29 *versus* 8 per cent; $P < 0{\cdot}05$).

The second study, from Bologna[36], randomized 111 patients without active variceal bleeding at the index endoscopy to either EIS (with polidocanol) or EVL. Similar eradication rates (93 per cent for EVL *versus* 92 per cent for EIS) were achieved, and fewer endoscopic sessions were required with EVL (mean(s.d.) 3·5(0·l) *versus* 4·0(0·1); $P < 0{\cdot}005$). However, in this study eradication took longer (33·8(2·1) *versus* 27·3(1·4) days; $P < 0{\cdot}01$) with EVL and, again, variceal recurrence was significantly greater in patients treated by band ligation (30 *versus* 13 per cent; $P < 0{\cdot}002$) with an increased relative risk of 2·90 (c.i. 1·06–7·93) for developing further varices. However, rates of rebleeding were similar (19 per cent for EIS and 16 per cent for EVL) and no survival advantage was demonstrated in favour of EVL in this study.

The key outcome variables of these seven studies are summarized in *Table 1*; significant differences in outcomes between treatment arms are highlighted.

Endoscopic variceal ligation for control of active bleeding

Band deployment and variceal ligation can be difficult in patients with active bleeding; large amounts of blood in the oesophagus decrease the field of view. In addition, blood and clot may fill the cylinder, further obscuring the endoscopist's view. The prospective studies described above, while not specifically addressing the effectiveness of variceal ligation in the presence of active bleeding, nevertheless collectively included almost 100 patients who were bleeding acutely when randomized to treatment with EVL. Results were encouraging, with cessation of bleeding reported in 80–100 per cent of cases. Stiegmann *et al.*[19] achieved control of acute bleeding in 12 of 14 patients with EVL compared to ten of 13 patients with EIS. Gimson *et al.*[21] reported control of acute bleeding in 19 of 21 patients with EVL and 21 of 23 patients with EIS. Other workers[20,22,34,35] have reported similar results, with control of acute bleeding in 80–100 per cent of patients with EVL and 77–89 per cent of patients with EIS. Although further outcome data are not available, these preliminary results suggest that EVL is as effective as EIS in the control of acute haemorrhage.

Following these observations, a prospective study formally evaluating the efficacy of EVL in acute bleeding was recently reported by Lo *et al.*[37]. Seventy-one patients with active variceal bleeding were randomized either to EVL (37 patients) or EIS (34). Cessation of bleeding was defined as no further bleeding within 72 h, and was achieved in 36 with EVL and 26 with EIS ($P = 0{\cdot}009$). EVL and EIS were equally effective at controlling oozing varices ($P = 0{\cdot}23$), but EVL was better at controlling spurting varices (94 *versus* 62 per cent; $P = 0{\cdot}012$). At 1-month follow-up rebleeding occurred in 17 per cent after EVL and 33 per cent after EIS ($P = 0{\cdot}19$); survival at 1 month was similar in both groups (mortality rate 19 per cent with EVL and 35 per cent with EIS; $P = 0{\cdot}19$), but morbidity was significantly lower with EVL (5 *versus* 29 per cent; $P = 0{\cdot}007$). This study demonstrates that EVL is highly effective in the presence of acute bleeding and should dispel the notion that a restricted view from the banding device might reduce the efficacy of the technique in active bleeding.

Combination therapy after variceal bleeding

Injection sclerotherapy of large varices may present technical difficulty. Large varices generally require greater sclerosant volume and often have needle puncture bleeding. They require more endoscopy sessions and have an increased associated risk of serious complication. Banding, on the other hand, is ideally suited to large varices. Small varices are easily injected but are often not suitable for banding as less tissue is available for trapping in the *O* rings. The concept of combining banding with sclerotherapy when varices are large and converting to injection sclerotherapy when smaller is appealing. EVL combined with low-dose injection sclerotherapy might achieve an improved variceal eradication and so reduce the likelihood of rebleeding.

Laine *et al.*[38] compared EVL with EVL plus sclerotherapy (EVL/EIS) in 41 patients. Twenty-one were randomized to the EVL/EIS treatment arm, in which ligation of the varix was followed by the injection of 1 ml 1·5 per cent sodium tetradecyl sulphate immediately above the ligature. However, the theoretical benefit was not realized in this study which reported similar eradication rates (60 and 71 per cent), rebleeding rates (30 and 29 per cent) and death rates (15 and 14 per cent) in the two groups. In addition, more treatment sessions (rather than fewer) were required to achieve eradication in the combined treatment arm, but no data were reported on the duration from index treatment to variceal eradication. It should be noted that varices were eradicated in all patients who underwent three treatment sessions (12 of 12 with EVL and 15 of 15 with EVL/EIS). However, EVL/EIS caused more complications than EVL alone (29 *versus*

10 per cent), particularly oesophageal stricture and ulceration.

Similar results were reported by Saeed *et al.*[39] who randomized 25 patients to EVL alone and 22 patients to EVL/EIS combination therapy. Control of acute bleeding, rebleeding rate, variceal eradication rate and mortality rate were similar in both groups. More endoscopy sessions were required to achieve eradication with combination therapy, which was associated with a higher incidence of deep mucosal ulceration, dysphagia and oesophageal stricture. These studies both suggest that little is to be gained by the addition of low-dose sclerotherapy to standard ligation techniques (*Table 2*).

This is confirmed in a study which compared EIS alone with combination EVL/EIS; there was a substantially higher variceal recurrence rate at 12-month follow-up in patients treated by combination therapy (39 *versus* 8 per cent; $P < 0{\cdot}05$)[40] (*Table 3*). However, 39 (64 per cent) of 61 patients in this study had their varices treated prophylactically and so a direct comparison with the other two studies[38,39] cannot be made. On current evidence, combination therapy (EVL/EIS) provides no additional benefit, is associated with a greater morbidity and cannot be recommended.

Endoscopic variceal ligation for prophylaxis in high-risk varices

A meta-analysis of all English language randomized controlled trials recommended that prophylactic sclerotherapy should not be applied widely[41], and this is the recommended policy in South Africa and the UK. Two prospective studies have evaluated EVL against a control group of patients to determine the efficacy for prevention of a first variceal bleed in patients with cirrhosis with high-risk varices. Sarin *et al.*[42] randomized 35 patients to prophylactic variceal eradication by EVL and 33 to no treatment. Fewer patients bled in the treatment group than in the control group during a mean follow-up of 14 months (9 *versus* 39 per cent; $P < 0{\cdot}01$). However, a high variceal recurrence rate of 29 per cent was noted after EVL and no survival benefit was observed following prophylactic eradication.

A later study by Lay and colleagues[43] reported a significant reduction in the rate of variceal haemorrhage after prophylactic EVL compared with that in control patients (19 *versus* 60 per cent; $P = 0{\cdot}001$) and a reduction in the cumulative 2-year mortality rate in the treatment group (28 *versus* 58 per cent; $P = 0{\cdot}001$). However, variceal recurrence was noted in 42 per cent after EVL and these recurrent varices were treated by sclerotherapy. The use of combined therapy in the treatment group makes interpretation difficult.

In the most recent study that investigated the role of prophylactic EVL in patients with high-risk varices, patients were randomized to treatment with EVL alone (18 patients), EIS alone (20) or a combination of EVL and EIS (21)[44]. During the study period of 24 months there was no death or acute variceal bleeding. Variceal recurrence was lowest in those treated by EIS (10 per cent), which was similar to that after combination therapy (12 per cent). Variceal recurrence was greatest after EVL alone, with varices detected in 40 per cent of patients. EIS was associated with an overall complication rate of 50 per cent (28 per cent due to dysphagia). It was concluded that combination therapy was the optimal prophylactic tech-

Table 2 Randomized trials comparing endoscopic band ligation with ligation plus sclerotherapy

Reference	Year	No. of patients	Treatment	No. of sessions*	Rebleed (%)	Variceal rebleeding (%)	Complications (%)	Recurrence (%)	Eradication (%)	Survival (%)
Laine *et al.*[38]	1996	20	EVL	2·7(0·4)	30	25	10	n.a	60	85
		21	EVL/EIS	4·9(0·6)†	29	19	29	n.a	71	86
Saeed *et al*[39]	1997	25	EVL	3·3(0·4)	25	86	25	16	n.a.	84
		22	EVL/EIS	4·1(0·6)	36	63	65†	23	n.a	64

*Values are mean(s.d.). EIS, endoscopic injection sclerotherapy, EVL, endoscopic variceal ligation, n.a , data not available. †$P < 0{\cdot}05$ *versus* EVL

Table 3 Randomized trial comparing endoscopic injection sclerotherapy with ligation plus sclerotherapy

Reference	Year	No. of patients	Treatment	No of sessions*	Rebleed (%)	Variceal rebleeding (%)	Complications (%)	Recurrence (%)	Survival (%)
Iso *et al.*[40]	1997	30	EIS	4·1(0·8)	0	n.a.	91	8	n.a
		31	EVL/EIS	3·0(0·5)	4	n.a	22†	39†	n.a

*Values are mean(s.d). EIS, endoscopic injection sclerotherapy, EVL, endoscopic variceal ligation, n.a., data not available †$P < 0{\cdot}05$ *versus* EIS nique as it achieved a longer duration of variceal eradication and an acceptable complication rate of 10 per cent. At present these data are insufficient to support the recommendation that EVL (alone or in combination) should be considered as appropriate prophylactic treatment for the prevention of bleeding in patients with high-risk varices.

Complications associated with endoscopic sclerotherapy and variceal ligation

EIS is associated with local and systemic complications which detract from the overall effectiveness of the technique. Minor complications occur frequently and are regarded as technique-related side-effects resulting from sclerosant injection. Examples include transient fever, retrosternal chest pain and short-term dysphagia, which occur in 50–60 per cent of patients[23]. However, more significant complications occur in approximately 20 per cent of patients after EIS, and the published procedure-related mortality rate is 0–5 per cent[26,45–48]. Local complications include oesophageal erosions and ulceration in 70–100 per cent, which may cause recurrent bleeding in 2–13 per cent[46]. Oesophageal perforation may occur from direct iatrogenic injury or oesophageal necrosis, and development of oesophageal strictures is reported in 7–59 per cent of patients[17,23,25]. Dissemination of sclerosant beyond the oesophagus may cause pleural effusion, pneumonia, systemic inflammatory response syndrome and septicaemia[24,46–52].

Oesophageal ulcers caused by EVL are more superficial and resolve faster than sclerotherapy-induced ulcers. EVL-induced bacteraemia occurs less often than after sclerotherapy and is associated with fewer episodes of significant infectious sequelae such as spontaneous bacterial peritonitis or pneumonia. Complications associated with the use of the overtube include oesophageal mucosal tears, variceal rupture with massive bleeding and oesophageal perforation[31,53,54]. Banding has also been associated with food impaction[54].

Despite the spectrum of EVL-induced complications, the overall incidence is substantially less than that associated with EIS. Stiegmann *et al.*[19] reported a complication rate of 2 per cent with EVL and 22 per cent with EIS. Fewer strictures and infective complications were noted after the former (neither statistically significant) and rebleeding rates were similar in the two groups. The study by Laine *et al.*[20] did not show a reduction in rebleeding with EVL, but demonstrated a significant reduction in stricture formation (none *versus* 33 per cent; $P < 0{\cdot}001$); infective complications were similar. Two subsequent studies[21,22] reported a reduction in variceal rebleeding rate after EVL, but this benefit was offset by an associated increased risk of rebleeding from ectopic varices and congestive gastropathy after EVL[22]. The benefits in favour of EVL reported by Lo *et al.*[22] (3 *versus* 19 per cent) and Baroncini *et al.*[36] (11 *versus* 33 per cent; $P = 0{\cdot}001$) were primarily a reduction in stricture formation. Overall, a significant reduction in procedure-related complications has been clearly demonstrated with EVL, and this alone is probably sufficient reason to recommend it in preference to EIS, as 50 per cent of the iatrogenic strictures induced by sclerotherapy cause significant morbidity and require repeated treatment by dilatation therapy[26,51,52].

Conclusion

The data accumulated from prospective randomized studies indicate that EVL ligation is as effective as EIS in the early management of bleeding oesophageal varices. However, control of active bleeding is superior with EVL and the incidence of rebleeding is lower. Furthermore, variceal eradication with EVL requires fewer endoscopic treatment sessions and causes substantially fewer local complications in the lower oesophagus.

Although the data demonstrate a reduction in early gastrointestinal rebleeding after EVL in most studies, this does not result in an overall survival benefit relative to EIS. However, the data currently available demonstrate clear advantages for using EVL in preference to EIS, and so EVL should be considered the endoscopic treatment of choice in the treatment of variceal haemorrhage.

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Promotion for randomized trials in the BJS

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Editorial Team of the BJS

Prospective randomized trial of end-to-end *versus* side-to-side biliary reconstruction after orthotopic liver transplantation

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Background: Biliary reconstruction is the Achilles heel of liver transplantation. Side-to-side anastomosis of donor and recipient bile duct has been claimed to be superior to end-to-end anastomosis in uncontrolled studies.

Methods: A total of 100 consecutive patients undergoing orthotopic liver transplantation were randomized after commencement of the transplant procedure to end-to-end or side-to-side anastomosis. No T tube drainage was employed. Endoscopic retrograde cholangiography was performed 2 weeks after transplantation and findings were reported by an experienced endoscopist as normal, leak or stricture. Median follow-up was 53 (range 35–63) months.

Results: Patient age, sex, the graft preservation time and indication for transplantation were similar in both groups. Sixty patients received end-to-end and 40 side-to-side anastomosis. Ten patients randomized to side-to-side anastomosis had an end-to-end procedure. The total number of biliary complications was similar in both groups (end-to-end 32 per cent *versus* side-to-side 30 per cent) as were the number of leaks (17 *versus* 18 per cent) and biliary strictures (15 *versus* 12 per cent). There was no difference in the number of biliary complications that required interventional treatment (22 per cent in both groups).

Conclusion: Side-to-side and end-to-end biliary anastomosis at liver transplantation are equally effective.

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Introduction

As the results of liver transplantation continue to improve, bile duct leaks or strictures remain one of the unsolved problems and are responsible for considerable morbidity, mortality and cost[1,2]. The mechanism of biliary complications following orthotopic liver transplantation (OLT) is often unclear. Bile duct ischaemia, immunological damage and preservation injury have all been implicated[3–5]. In the evolution of clinical liver transplantation many approaches have been used for reconstruction of the biliary tree. Use of the gallbladder as a vascularized conduit was associated with a high incidence of late stricture and cholangitis[6,7]. Most centres have adopted a direct end-to-end anastomosis of donor and recipient bile duct with drainage externally via a T tube[8,9]. However, side-to-side bile duct anastomosis with T tube drainage was reported in a single-centre experience[10] to provide superior results to those generally reported[11]. Many centres have reported successful biliary reconstruction without the use of T tubes and their associated complications[12,13], although results from controlled studies are conflicting[14,15]. A prospective single-blind randomized controlled trial of end-to-end *versus* side-to-side biliary reconstruction without T tube drainage following OLT was therefore performed.

Patients and methods

Between August 1992 and January 1995, 100 consecutive patients undergoing OLT at the Royal Free Hospital were randomized to receive end-to-end or side-to-side duct-to-duct biliary anastomosis without T tube drainage. The trial size was based on demonstrating a difference in biliary complication rate between the 1 per cent incidence reported for side-to-side anastomosis by Neuheus and colleagues[10] and the 10–20 per cent rate with end-to-end anastomosis reported by the present authors[13] and others[10,12]. To give a power of 90 per cent and a significance of 0·05, 50 patients were required in each arm. Randomization was by a consecutively numbered sealed-envelope system. The operating surgeon was unaware of the type of biliary reconstruction to be performed until operation began and the patients were not informed of which anastomosis had been fashioned. Patients who were considered for primary Roux-en-Y loop reconstruction were excluded from the randomization, including those undergoing retransplantation.

Ethics committee approval for this study was not sought as the techniques of reconstruction are both accepted as standard methods. All patients in the authors' unit routinely undergo postoperative endoscopic retrograde cholangiography (ERC) to demonstrate the anastomosis.

Donor livers were harvested according to a standard protocol and preserved on ice with lactobionate–raffinose preservation solution. The age, sex and indications for transplantation of the recipients were recorded along with the cold ischaemia time for grafts. Biliary anastomosis was performed after venous and arterial revascularization of the graft. The donor and recipient bile ducts were mobilized sufficiently to allow biliary anastomosis but preservation of ductal blood supply. The end-to-end anastomosis was performed with interrupted 5/0 polydioxanone sutures. Two consultant transplant surgeons performed the majority of biliary reconstructions, the others being carried out by experienced trainees under direct consultant supervision. For side-to-side anastomosis the duct ends were ligated and 2 cm of donor and recipient duct proximal to the ligatures was brought into apposition. A 1–1·5-cm lateral choledochotomy was made on the donor and recipient bile duct. Anastomosis was performed with 5/0 continuous polydioxanone suture.

Immunosuppression was unchanged over the study period and consisted of triple therapy of cyclosporin (4 mg kg^{-1} day^{-1} intravenously then 10 mg kg^{-1} day^{-1} orally), steroids (methylprednisolone 0·8 mg kg^{-1} day^{-1}) and azathioprine (1·5 mg kg^{-1} day^{-1}). Acute rejection episodes were treated with 1 g methylprednisolone intravenously on 3 consecutive days. All patients, regardless of the clinical course, were scheduled to have ERC 2 weeks after OLT. Further cholangiography was performed if clinically indicated. ERC was performed with Olympus TJF-10 and JFIT10 scopes (Keymed, Southend, UK) under antibiotic cover (mezlocillin, 2 g intravenously; Newbury, Bayer, UK).

Results were reported by two experienced endoscopists as normal, leak or stricture. A patient was considered to have a biliary complication if cholangiography showed a stricture or leak regardless of its extent or severity. The decision about further treatment was based on the size of the stricture or leak, the patient's clinical condition and liver function test results. Patients who were clinically well with stable graft function and cholangiography showing a small anastomotic leak or stricture were treated expectantly. Patients with large leaks on cholangiography, strictures with proximal ductal dilatation, cholestatic liver function or who were clinically symptomatic had endoscopic or surgical intervention.

The total number of biliary complications, including strictures and leaks, was recorded along with the method of treatment. Biliary complications were grouped into those diagnosed within 30 days of OLT, within the first 3 months and late complications (more than 3 months after OLT). Follow-up was available for all surviving patients, for a median of 53 (range 35–63) months. Survival values for the perioperative period and at 3 months and 1 year were calculated.

Results were analysed according to intention to treat and treatment received. Mann–Whitney U and χ^2 tests were used to compare groups. Values are expressed as median (range).

Results

One hundred consecutive patients undergoing liver transplantation were randomized to have either end-to-end or side-to-side biliary anastomosis. Twenty patients were excluded from the trial because they were undergoing retransplantation or a primary Roux en Y loop reconstruction. Ten patients were randomized to side-to-side anastomosis but had an end-to-end procedure performed because the operating surgeon considered that there was insufficient length of donor and/or recipient bile duct to allow a side-to-side anastomosis without tension. There were no conversions after commencement of the biliary anastomosis. No patient randomized to end-to-end anastomosis was converted to a side-to-side procedure. Therefore 60 patients had end-to-end and 40 had side-to-side anastomoses. The side-to-side anastomosis was found to take longer than the end-to-end procedure, but the exact operating time was not recorded.

The data were analysed as both 'intention to treat' and 'treatment received'. The groups were well matched for recipient age, sex and the cold preservation period of the graft (*Table 1*). Indications for transplantation are shown in *Table 2*. Patients with primary sclerosing cholangitis in whom significant stricturing of the distal extrahepatic bile duct was found at the time of surgery underwent primary Roux-en-Y loop reconstruction and were not randomized. Those without distal strictures were randomized. In most aetiological groups the type of biliary reconstruction was well balanced, apart from patients with primary biliary

Table 1 Patient age, sex and graft cold ischaemia time

	Intention to treat		Treatment received	
	E-E	S-S	E-E	S-S
No. of patients	50	50	60	40
Age (years)*	49 (6–62)	46 (18–63)	48 (6–68)	48 (22–63)
Sex ratio (M : F)	33 : 17	33 : 17	40 : 20	26 14
Cold ischaemia time (min)*	760 (358–1227)	758 (210–1210)	769 (322–1227)	750 (210–1210)

*Values are median (range). E-E, end-to-end bile duct anastomosis, S-S, side-to-side bile duct anastomosis. There were no significant differences between the groups

Table 2 Indications for liver transplantation

	Intention to treat		Treatment received	
	E-E (*n* = 50)	S-S (*n* = 50)	E-E (*n* = 60)	S-S (*n* = 40)
Hepatitis C	14	17	17	14
Alcoholic cirrhosis	10	7	11	6
Primary sclerosing cholangitis	7	9	9	7
Primary biliary sclerosis	9	3	10	2
Other*	10	14	13	11

*Other (*n* = 24) included cryptogenic cirrhosis (six patients), hepatitis B or D cirrhosis (four), Caroli's disease (one), fulminant non-A non-B hepatitis (four), Budd–Chiari syndrome (three), autoimmune chronic active hepatitis (two), chronic rejection (three) and amyloidosis (one). E-E, end-to-end bile duct anastomosis; S-S, side-to-side bile duct anastomosis

Table 3 Comparison of biliary complications

	Intention to treat		Treatment received	
	E-E (*n* = 50)	S-S (*n* = 50)	E-E (*n* = 60)	S-S (*n* = 40)
Leak	9 (18)	8 (16)	10 (17)	7 (18)
Stricture	7 (14)	7 (14)	9 (15)	5 (12)
Total	16 (32)	15 (30)	19 (32)	12 (30)
Complications requiring treatment	11 (22)	11 (22)	13 (22)	9 (22)

Values in parentheses are percentages. E-E, end-to-end bile duct anastomosis, S-S, side-to-side bile duct anastomosis

cirrhosis, the majority of whom received end-to-end anastomosis. This unintentional bias was present in both intention to treat and treatment received analyses (*Table 2*).

Biliary complications are shown in *Table 3*. These have been divided into early (30 days or fewer after transplantation), intermediate (after day 30 but within 3 months) and late (more than 3 months). Length of follow-up ranged from 35 to 63 (median 53) months. Approximately 30 per cent of patients had a biliary tract complication, which was similar in the patient group receiving end-to-end anastomosis (32 per cent) and that receiving side-to-side anastomosis (30 per cent). This value was unchanged by the method of data analysis. Postoperative cholangiography was performed routinely in this study 2 weeks after OLT. Nine of the 31 patients considered as having a 'biliary tract complication' were diagnosed on the findings of cholangiography alone and did not require any treatment. There was no difference between the end-to-end and side-to-side groups when only biliary complications requiring treatment were considered (22 per cent for both groups). Analysis of the type of biliary complication revealed leaks and strictures to have a similar incidence in the two types of biliary reconstruction.

Ninety-one of the 100 biliary reconstructions were carried out by one of two consultant transplant surgeons and nine by trainees under supervision. There was no significant difference in the overall biliary complication rate between the two consultant surgeons (12 (29 per cent) of 42 *versus* 19 (37 per cent) of 49), nor in the complication rate for end-to-end (seven (29 per cent) of 24 *versus* 12 (38 per cent) of 32) or side-to-side (five (28 per cent) of 18 *versus* seven (41 per cent) of 17) anastomosis.

Bile leaks and their treatment are shown in *Table 4*. The majority of bile leaks were managed by further

Table 4 Bile leaks and their treatment

	No. of leaks
End-to-end group (*n* = 10)	
No treatment required	4
Roux-en-Y loop	5
T tube	1
Side-to-side group (*n* = 7)	
No treatment required	2
Roux-en-Y loop	3
Anastomotic suturing	1
Endoscopic stent	1

Table 5 Biliary strictures and their treatment

	No. of strictures
End-to-end group (*n* = 9)	
No treatment	2
Roux-en-Y loop	5
Nasobiliary	1
Repeat OLT	1
Side-to-side group (*n* = 5)	
No treatment	1
Roux-en-Y loop	2
T tube	1
Nasobiliary	1

OLT, orthotopic liver transplantation

laparotomy and conversion of the duct-to-duct anastomosis to a choledochojejunostomy using a Roux-en-Y loop. Initial treatment of the bile leak in those requiring intervention was by endoscopic or percutaneous drainage in four of the ten patients in the end-to-end group and in two of the seven in the side-to-side group. No early deaths in either group were related to the bile duct leak. In the end-to-end group there was one death from multiple organ failure 2 months after transplant and in the side-to-side group there was one death at 2 months from a brainstem haemorrhage. All other patients with bile leaks were discharged from hospital alive and well.

Biliary strictures occurred in nine (15 per cent) of the 60 patients with end-to-end anastomosis and in five (12 per cent) of the 40 with side-to-side anastomosis. The treatment of these complications is shown in *Table 5*. No intervention was necessary in two of nine patients in the end-to-end group and in one of five of the side-to-side group. Again the standard treatment for this complication was laparotomy and conversion to a choledochojejunostomy using a Roux-en-Y loop. One patient in each group responded to a period of nasobiliary drainage and did not require further biliary tract intervention. Retransplantation for one patient in the end-to-end group was carried out 13 months after OLT for biliary stricturing associated with hepatic arterial thrombosis. Of the nine patients with strictures in the end-to-end group, three had initial management by endoscopic or percutaneous drainage, and in one of the five patients with side-to-side anastomosis. Three of the nine patients with biliary tract strictures in the end-to-end group died, and one of the five in the side-to-side group (*P* not significant). Deaths were unrelated, apart from one death in the end-to-end group which was due to biliary tract sepsis.

Table 6 Timing of biliary leak with respect to the method of anastomosis

	Interval after liver transplantation		
Group	≤ 30 days	30 days to 3 months	> 3 months
E-E	7 of 10	3 of 10	0
S-S	5 of 7	2 of 7	0

E-E, end-to-end bile duct anastomosis, S-S, side-to-side bile duct anastomosis

Table 7 Timing of biliary stricture with respect to the method of anastomosis

	Interval after liver transplantation		
Group	≤ 30 days	30 days to 3 months	> 3 months
E-E	2 of 9	3 of 9	4 of 9
S-S	2 of 5	1 of 5	2 of 5

E-E, end-to-end bile duct anastomosis; S-S, side-to-side bile duct anastomosis

Bile leaks occurred mainly within the first 30 days following OLT in both groups (seven of ten for end-to-end *versus* five of seven for side-to-side anastomosis) (*Table 6*). In contrast, strictures occurred mainly after the first 3 months in both groups (four of nine in the end-to-end group *versus* two of five in the side-to-side group) (*Table 7*). Of the 100 randomized patients, 34 have died within the follow-up period. At the end of 3 months, 51 (85 per cent) and 31 (78 per cent) were alive in the end-to-end and side-to-side groups respectively. The 1-year survival rate was 72 per cent for both groups (43 of 60 and 29 of 40 respectively).

Discussion

This is the first controlled trial of biliary reconstruction following OLT. The rationale for the study was the low biliary complication rates obtained in single-centre experiences with side-to-side biliary reconstruction[10,11]. This trial has shown no evidence that side-to-side reconstruction is preferable in terms of complications. The single-blind nature of the study and analysis by both intention to treat and treatment received prevented bias in patient selection, the donor organs, their preservation, the surgical technique employed or in data analysis.

The trial size (100 randomized patients) was designed to show a difference in the rate of biliary complications (leaks and strictures) based on the largest single-centre experience of side-to-side reconstruction from the Berlin group[10] (0·3 per cent for leaks and 0·6 per cent for strictures) and the results reported from the present authors' centre[13] (11 per cent for leaks and 11 per cent for strictures), which are similar to those of others routinely employing end-to-end choledochocholedochostomy without T tube drainage[12]. The authors' previously reported incidence of biliary tract complications is also similar to that found in a collective review of end-to-end anastomosis using T tube drainage reported by Neuheus *et al.*[10] (184 (25 per cent) biliary complications in 729 patients).

Many factors are involved in the production of biliary complications after OLT. As with any surgical procedure, technical factors are important but analysis of complications by the operating surgeon showed no significant differences in the present study. The association with repeated cellular rejection and the higher incidence with ABO unmatched grafts[4] suggests that immunological factors may play a role in some cases. An association with prolonged graft cold preservation time has been reported[5] and the biliary complications seen with hepatic arterial occlusion would implicate ischaemia[4]. The present study and a previous study by the authors[13] showed that patients coming to biliary reconstruction following OLT usually have extensive duct necrosis rather than a local anastomotic problem, suggesting that the biliary tract problem is one of donor duct ischaemia. A controlled trial allows the type of biliary anastomosis alone to be analysed as a variable, and this study suggests that the type of biliary anastomosis is of little relevance to the incidence of biliary tract complications.

One factor that may be important in the excellent results in the series of side-to-side biliary reconstruction by Neuheus *et al.*[10] is the use of T tubes to stent across the anastomosis and provide external biliary drainage. A specially designed small-bore T tube was employed routinely which stented across the anastomosis and was brought out distal to the anastomosis. T tubes were not used in the present study as the authors previously found no benefit to their use in a retrospective uncontrolled study[13]. Many other centres have similarly abandoned the routine use of T tube drainage[12,16]. However, biliary tract pressures may be raised following liver transplantation[17], associated with sphincter of Oddi dysfunction[18]. The value of biliary decompression requires further study as two randomized controlled studies on the use of T tubes following liver transplantation have produced conflicting conclusions, one supporting[14] and the other recommending abandonment[15] of the use of T tubes.

One difficulty of the side-to-side as opposed to the end-to-end anastomosis is that a greater length of bile duct is required to allow the overlap of bile duct necessary to perform the side-to-side anastomosis. For this reason a significant number of patients randomized in the trial to a side-to-side anastomosis had end-to-end biliary reconstruction. The additional mobilization required for side-to-side anastomosis may have been expected to result in greater bile duct ischaemia and hence increased ischaemic biliary complications[19–21]. However, recipient bile duct necrosis was not seen in the present study, suggesting that duct mobilization in the recipient is safe and does not increase duct ischaemia as has previously been suggested[19–21]. Because T tubes were not inserted in the recipient bile duct, duct mobilization may have been less than would be required for T tube insertion. Of interest, ampullary dysfunction producing biliary obstruction, which is a frequently reported complication of the previous studies on side-to-side anastomosis with T tube drainage[10], was not found in the present series. This may relate to the reduced ductal mobilization.

The operating time required for side-to-side anastomosis was longer in the present study than that for end-to-end anastomosis. This was not, however, evaluated objectively in the study as it was not considered to be an important factor in relation to the time required for the liver transplant procedure.

The incidence of treated biliary tract complications in the present series (22 per cent) was high in comparison to some reported series, but was within a commonly reported range[10]. The incidence of leaks and strictures was similar between the two treatment groups. The longer anastomosis with the side-to-side ductal reconstruction neither reduced anastomotic narrowing nor increased leakage. The similarity in biliary complication rates also suggests that local technical problems are not fundamental to these biliary complications.

A novel and essential aspect to this study was the protocol cholangiography that was performed about 10–14 days after operation. The authors have found ERC to be a safe and effective method of diagnosing biliary complications following OLT[22]. Biliary scintigraphy may also be valuable as a screening investigation for biliary tract complications, but in a prospective trial the authors found cholangiography to be required to establish the nature of the biliary problem[23]. Having a protocol biliary tract investigation avoids complications being overlooked, but may increase surgical or radiological intervention. The clinical value of protocol cholangiography needs to be critically assessed. The value of endoscopic or percutaneous intervention for the treatment of biliary complications following OLT[22,24] also requires properly controlled prospective studies, bearing in mind the excellent results of surgical intervention with Roux-en-Y reconstruction[25].

In conclusion, there are no differences in short-term outcome or long-term follow-up for patients having side-to-side rather than end-to-end biliary reconstruction following liver transplantation. Further controlled studies are required to determine the factors important for biliary tract complications.

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Original article

Noradrenaline improves the tumour to normal blood flow ratio and drug delivery in a model of liver metastases

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Background: Vasopressors administered via the hepatic artery appear to increase drug delivery to colorectal liver metastases, but are limited by a short duration of action. This study measured their effect on blood flow and drug delivery during a prolonged infusion in a model of liver metastases.

Methods: In Hooded Lister rats with liver metastases, blood flow in tumour and adjacent normal liver was measured using laser Doppler flowmetry during a 30-min hepatic arterial infusion of endothelin 1, angiotensin II, vasopressin, *N*-nitro-L-arginine methyl ester (L-NAME), noradrenaline or saline ($n = 6$ per group). The same agents were co-administered with radiolabelled 5-fluorouracil (5-FU) ($n = 6$ per group) and uptake in the tumour and normal liver was measured.

Results: The mean(s.d.) duration of effect and resulting percentage changes in tumour to normal blood flow ratio of the vasopressors during this period were: noradrenaline, 2·9(0·4) min and 34(5) per cent ($P < 0{\cdot}05$); angiotensin II, 4·2(0·2) min and 10(2) per cent ($P < 0{\cdot}05$); vasopressin, 11·1(0·9) min and 7(2) per cent ($P < 0{\cdot}05$); endothelin 1, 21·5(2·3) min and 14(5) per cent ($P < 0{\cdot}05$); and L-NAME, 22·6(3·3) min and 2(1) per cent (P not significant). The mean(s.d.) uptake of radiolabelled 5-FU by the tumour in the groups studied was: saline, 5·1(3·2) $\times 10^5$ c.p.m. per g tissue; angiotensin II, 5·1(1·4) $\times 10^5$ c.p.m. per g; endothelin 1, 15·8(14·2) $\times 10^5$ c.p.m. per g; L-NAME, 3·5(1·3) $\times 10^5$ c.p.m. per g; and vasopressin, 6·8(3·5) $\times 10^5$ c.p.m. per g. Significant improvements in 5-FU uptake only resulted from noradrenaline infusion (22·0(9·8) $\times 10^5$ c.p.m. per g; $P < 0{\cdot}05$).

Conclusion: These findings suggest that hepatic arterially infused noradrenaline might be used to improve drug delivery to liver metastases.

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Introduction

Hepatic arterial chemotherapy produces a higher loco-regional response rate than conventional systemic chemotherapy in patients with colorectal liver metastases. Initial clinical studies suggest this may translate into improved survival[1,2] and enhanced quality of life[3]. The rationale behind this route of therapy is that liver metastases receive up to 95 per cent of their blood supply via the hepatic artery, so a greater proportion of a chemotherapeutic agent will be delivered to the tumour.

Further improvements in drug delivery might be achieved by a greater understanding of the differences that exist between tumour and normal hepatic vessels. Using electron microscopy it is apparent that blood vessels within colorectal liver metastases lack both innervation and a developed smooth muscle coat[4]. As such these 'tumour' blood vessels are unlikely to possess any significant neurogenic vasoconstrictor capability.

Appreciation of this observation may allow selective vasoconstriction of normal hepatic vessels while leaving tumour vessels unaffected. This in turn should lead to shunting of blood into the tumour with a concomitant improvement in drug delivery. Regionally infused vasopressors improve the uptake of chemotherapeutic agents by liver metastases presumably by enhancing tumour blood flow[5]. However, their short duration of action is a limiting factor.

In order to assess the mechanism and efficacy of regionally infused vasopressors, an animal model of colorectal liver metastases, in which tumour blood vessels have a similar anatomical and physiological profile to those in human colorectal liver metastases[6,7], has been developed.

Materials and methods

Experiments were performed using male Hooded Lister rats (350–400 g) which 14 days previously had undergone intraportal inoculation of 1×10^6 MC28 syngeneic tumour cells. This produced between two and five tumours per rat measuring from 5 to 8 mm on the liver surface. Seventy-two animals then underwent laparotomy under halothane anaesthesia and the gastroduodenal artery was cannulated with fine-bore tubing (Portex UK, Hythe, UK) using an operating microscope[8].

All animal work was carried out under Home Office approval.

Blood flow measurements

Microcirculatory blood flow was measured using laser Doppler flowmetry (MBF3D; Moor instruments, Axminster, UK). The probe design allows measurement up to a depth of 2 mm and the flow values are expressed in arbitrary flux units which are proportional to microcirculatory blood flow. Before each experiment the probe was recalibrated and a time constant of 3·0 s at 0·25 Hz was used to minimize movement artefact.

A probe measuring 30 × 1 mm was placed over the centre of the tumour in a specially designed holder and another was placed on an area of adjacent normal liver within the same lobe but 2 cm away. To minimize pressure from the holder and probe the wire was suspended from a clamp. The laparotomy wounds were closed to prevent drying of the liver surface and the core temperature was maintained using a heated mat.

Each rat was infused for 30 min with one of the vasopressors listed below and baseline measurements were taken for 5 min before and after infusion.

All data were collected and analysed using the Maclab PC data logging system (Apple, Cupertino, California, USA). The duration of effect and flow changes, as demonstrated by the areas under the flux line curves, were calculated.

Regionally infused vasoconstrictors

Thirty-six rats were divided into six groups ($n = 6$ in each) and each group received a different agent. Agents were prepared in 0·9 per cent saline before each experiment and kept at rat core temperature before infusion. The dose of agent chosen was that which produced a 20 per cent rise in systemic blood pressure. Agents were infused over 30 min (in a volume of 1 ml) using an infusion pump (Harvard, Cambridge, Massachusetts, USA) into the hepatic artery via the gastroduodenal artery.

The agents used were: *N*-nitro-L-arginine methyl ester (L-NAME) 1·5 mg per kg per min, noradrenaline 5 μg per kg per min, vasopressin 1 μg per kg per min, endothelin 1 0·5 μg per kg per min, angiotensin II 0·35 μg per kg per min and saline in the control group. All vasoactive agents were purchased from Sigma (Poole, UK).

Radiolabelled 5-fluorouracil

Another group of rats ($n = 36$), 14 days after intraportal inoculation of MC28 tumour, underwent cannulation of the gastroduodenal artery. Identical doses of the same vasopressors in conjunction with [^{3}H]5-fluorouracil (5-FU) were infused in 1 ml over 30 min ($n = 6$ in each group). At the end of this period the animals were killed and the livers were removed.

Tumour and liver from the same lobe (taken 2 cm away from the tumour) were removed and weighed. The tissue was solubilized and diluted in scintillant (Toluene Scintillator; Packard, Reading, UK). Samples were radiocounted and values expressed as counts per gram of tissue per minute.

Statistical analysis

The data underwent one-way analysis of variance followed by unpaired t test corrected for unequal variances. A probability of $P < 0.05$ was considered significant.

Results

Laser Doppler flow

The tumour to normal blood flow ratio (T : N) before commencing the infusions ranged between 0·25 and 0·35 (mean 0·30) which is similar to that found in human colorectal liver metastases.

All vasopressors studied produced a variable drop in flux measurement in both tumour and normal liver; all agents apart from L-NAME produced almost immediate effects and the time course in both tumour and liver was equal. None of the agents produced an absolute rise in tumour blood flow.

The percentage changes in the T : N ratio during the infusion periods can be considered in two ways. First, when taken over the whole 30-min infusion period, none of the agents produced a significant change. However, if the period in which the agent had its effect is considered

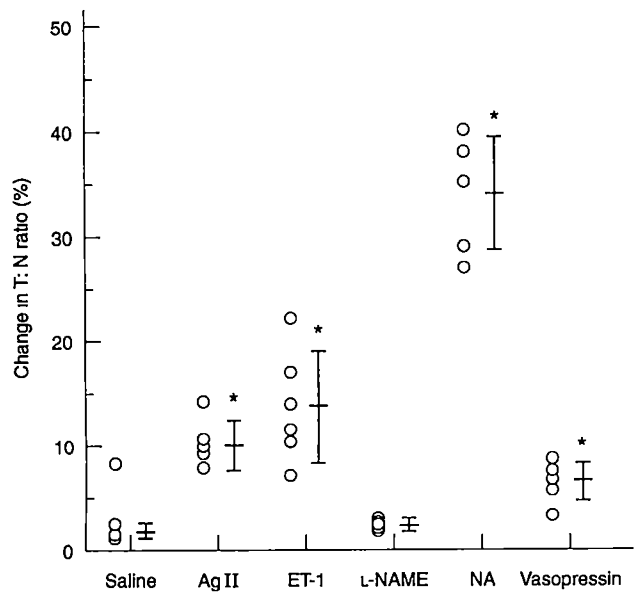

Fig. 1 Percentage change in tumour to normal blood flow (T : N) ratio during the effective period of vasoconstriction in the presence of normal saline (control group), angiotensin II (Ag II), endothelin 1 (ET-1), *N*-nitro-L-arginine methyl ester (L-NAME), noradrenaline (NA) and vasopressin. Bars are mean(s.d.) values ($n = 6$ per group). *$P < 0\cdot05$, unpaired t test corrected for unequal variances

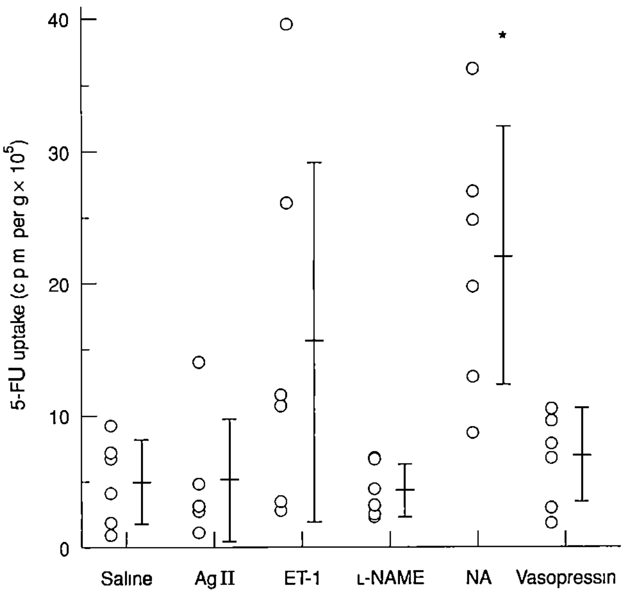

Fig. 3 Uptake of $[^3\text{H}]$5-fluorouracil (5-FU) in tumour, under the influence of vasoconstrictors or saline. Radioactive 5-FU was co-infused with different vasoconstrictor agents in the tumour-bearing livers of rats. Bars are mean(s.d.) values ($n = 6$ per group). Ag II, angiotensin II; ET-1, endothelin 1; L-NAME, *N*-nitro-L-arginine methyl ester; NA, noradrenaline. *$P < 0\cdot05$, unpaired t test corrected for unequal variances

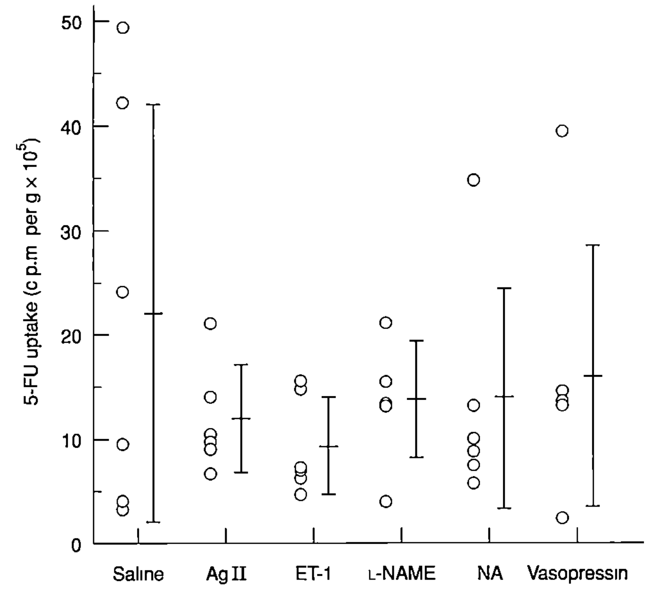

Fig. 2 Uptake of $[^3\text{H}]$5-fluorouracil (5-FU) in normal liver, under the influence of vasoconstrictors or saline. Radioactive 5-FU was co-infused with different vasoconstrictor agents in the tumour-bearing livers of rats. Bars are mean(s.d.) values ($n = 6$ per group). Ag II, angiotensin II; ET-1, endothelin 1; L-NAME, *N*-nitro-L-arginine methyl ester; NA, noradrenaline

separately (as defined as the period taken for the flux lines to return to the original preinfusion point) the mean(s.d.) percentage change in T:N ratio and duration of action were as follows: angiotensin II, 10(2) per cent ($P < 0\cdot05$) and 4·2(0·2) min; noradrenaline, 34(5) per cent ($P < 0\cdot05$) and 2·9(0·4) min; vasopressin, 7(2) per cent ($P < 0\cdot05$) and 11·1(0·9) min; endothelin 1, 14(5) per cent ($P < 0\cdot05$) and 21·5(2·3) min; and L-NAME, 2(1) per cent (P not significant) and 22·6(3·3) min. Changes in the T:N ratio are illustrated in *Fig. 1*.

$[^3\text{H}]$5-fluorouracil uptake

None of the agents produced a significant difference in the uptake of $[^3\text{H}]$5-FU in normal liver compared with the saline group (*Fig. 2*). Mean(s.d.) uptake into the tumour was as follows: saline, 5·1(3·2) × 10^5 c.p.m. per g tissue; angiotensin II, 5·1(1·4) × 10^5 c.p.m. per g; endothelin 1, 15·8(14·2) × 10^5 c.p.m. per g; L-NAME, 3·5(1·3) × 10^5 c.p.m. per g; noradrenaline, 22·0(9·8) × 10^5 c.p.m. per g; and vasopressin, 6·8(3·5) × 10^5 c.p.m. per g. Noradrenaline was the only agent to produce a significant increase in radiolabelled 5-FU uptake in the tumour ($P < 0\cdot05$) as illustrated in *Fig. 3*.

Discussion

Differences between blood vessels in tumour and normal hepatic tissue were first suggested in 1969[9]. More recently, using electron microscopy and immunohistochemistry, blood vessels in colorectal liver metastases were shown to lack both a complete smooth muscle wall and neuronal innervation[4]. A similar profile has been demonstrated in the blood vessels supplying MC28 tumours, suggesting a comparable situation to that in humans[6,7].

These findings lend support to the hypothesis that selective vasoconstriction of normal, but not tumour, hepatic vessels achieved by the administration of regionally infused vasopressors would result in blood being shunted from the hepatic vascular bed into the tumour and hence improve drug delivery.

Adrenaline has long been known to improve the tumour blush in hepatic angiography of colorectal liver metastases, beyond that which might be expected from vasoconstriction of normal surrounding vessels alone. Noradrenaline has been shown to produce increased uptake of radiolabelled microspheres when co-administered in conjunction with propanolol via the hepatic artery in an animal model[10], although its duration of action was limited. Ackerman *et al.*[11] demonstrated increased capillary blood flow, using laser Doppler flowmetry, within intrahepatic tumours due to infused catecholamines in an animal model. Goldberg and colleagues[12] demonstrated improved uptake of radioactive tracers with angiotensin II in patients with colorectal liver metastases receiving hepatic arterial chemotherapy. Use of intraoperative laser Doppler in patients with colorectal liver metastases has demonstrated improved tumour blood flow when angiotensin II was administered via the hepatic artery[5]. It has been suggested that part of the effect is due to the increased systemic blood pressure and hence increased tumour perfusion pressure, producing a subsequent opening up of tumour vessels. This is unlikely, however, as the changes in pressure do not mirror the changes in tumour blood flow demonstrated. Dworkin *et al.*[13], using an animal model, demonstrated improvements in the T:N ratio of intrahepatic tumours using vasopressin with and without a nitric oxide synthase inhibitor. The results of this study suggest that addition of such inhibitors prolongs the effect of vasopressin and implicates nitric oxide production within hepatic vessels as a possible cause of the limited duration of action seen with hepatic arterially infused vasopressors. Using the same animal model, Dworkin *et al.*[14] demonstrated that although hepatic arterially infused angiotensin II led to improvement in the T:N ratio it did not lead to a significant improvement in drug uptake. A similar study demonstrated that only endothelin 1 produced a significant improvement in the T:N ratio when infused over 30 min[15].

One of the limitations of most studies to date is that vasopressors have been given as either a bolus or short infusion. Given that hepatic arterial chemotherapy is administered over a prolonged period, assessment of the action of regionally infused vasopressors over this time course would be required before contemplating a clinical trial.

This study confirms the limited duration of action of vasopressors seen previously[13–15] and illustrates their ability to raise the T:N ratio. The reduction in blood flow seen in the tumour circulation (although less than that in the liver) might be due to constriction of feeding vessels coming from the normal adjacent liver or might represent an element of tumour vessel constriction.

Downregulation of sympathetic innervation in tumour vessels[4,7] might explain why noradrenaline (a sympathetic neurotransmitter) produced the greatest rise in the T:N ratio. If noradrenaline receptors were downregulated to a greater extent than those for other neurotransmitters then its administration would lead to less intrinsic tumour vessel constriction and hence produce a greater increase in the T:N ratio.

Other groups have demonstrated improved drug uptake and blood flow in hepatic tumours using endothelin 1, angiotensin II and vasopressin. The animal studies involving these agents used different tumours to the one employed in this study which may account for the different results reported here. It should be noted that the blood vessels found within MC28 tumours possess a similar profile with regard to both structure and innervation to those found in human colorectal liver metastases[4,7]. The dose used is relevant when comparing the results of this study with those from similar investigations in animal and humans. Many of these studies used higher doses of vasopressors than described here, and produced sustained marked hypertension (greater than the 20 per cent level in this study). Such effects would be unacceptable in a clinical setting. These variations in doses may account for the greater effectiveness noted for agents such as angiotensin II in similar reported studies.

As none of the agents produced improvements in tumour blood flow in real terms it is surprising that noradrenaline caused an increased uptake of radiolabelled 5-FU in the tumours. Jain[16] demonstrated that such tumours exist in a state of interstitial hypertension, which retards the movement of molecules such as chemotherapeutic agents through the interstitium. This interstitial hypertension leads to radially outward convection within the tumour periphery which opposes inward diffusion. Part of the effect produced by these vasopressors might be a reversal of the pressure gradient around the tumour leading to improved drug delivery. Since noradrenaline produced the greatest change in the T:N ratio it may be the only agent to have passed the threshold required to reverse the gradient. If the main action is achieved through pressure changes rather than shunting, then this may explain why uptake in the normal liver was unaffected.

Vasopressors increase the T:N ratio and noradrenaline specifically improves drug delivery when co-administered with hepatic arterial chemotherapy. However, as hepatic arterial chemotherapy is usually given as a prolonged infusion the limited duration of action of the vasopressors studied may preclude their use in a clinical setting. A greater understanding of their pharmacokinetic profile, especially with regard to the refractory period, may allow incorporation of these agents into a regional chemotherapeutic trial.

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Original article

Interleukin 6 in bile as an indicator of liver function after hepatectomy in patients with biliary tract carcinoma

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Background: Interleukin (IL) 6 is one of the important components of the early signalling pathways leading to liver regeneration, and has been detected in the bile after liver transplantation. IL-6 concentrations in the bile were studied in an attempt to predict liver function after major hepatectomy for biliary tract carcinoma.

Methods: This study involved 24 patients without cirrhosis who underwent major hepatectomy for biliary tract carcinoma. The bile was sampled regularly through external biliary drainage tubes. IL-6 concentrations in bile and serum were measured using an enzyme-linked immunosorbent assay.

Results: Bile IL-6 concentrations increased 37-fold (from mean(s.e.) 56(13) pg/ml before hepatectomy to 2071(398) pg/ml on day 1 after operation) in patients without liver failure after hepatectomy ($n = 18$) and increased sevenfold (from 71(24) to 530(76) pg/ml) in patients with liver failure after hepatectomy ($n = 6$). The values were significantly lower in patients with liver failure than in those without liver failure ($P < 0.05$). The bile IL-6 concentration on day 1 after operation exhibited a significant negative correlation with the maximum serum total bilirubin concentration after hepatectomy. Although serum IL-6 concentrations were also increased in both groups after hepatectomy, there was no significant correlation with postoperative liver function.

Conclusion: Increased bile IL-6 concentrations after hepatectomy may reflect liver regenerative capacity. Measurement of bile IL-6 concentrations may be clinically useful for the early identification of liver failure after hepatectomy.

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Introduction

Liver regeneration stimulated by a loss of liver mass leads to hepatocyte and non-parenchymal cell proliferation and rapid restoration of the hepatic parenchyma[1–3]. Interleukin (IL) 6 is a multifunctional protein produced by T cells, monocytes[4], macrophages[5], Kupffer cells[6], fibroblasts[7], vascular endothelial cells[8] and several other cell lines[9]. IL-6 plays an important role in stimulating the production of acute-phase reactants from hepatocytes, including C-reactive protein (CRP)[10]. It has also been reported that IL-6 is one of the important components of the early signalling pathway contributing to the proliferation of hepatocytes and leading to liver regeneration[11–13]. In humans, serum IL-6 concentrations have been shown to increase after hepatectomy and other operative procedures[14,15]. Using an enzyme-linked immunosorbent assay (ELISA), Umeshita *et al.*[16] have detected IL-6 excretion in the bile after liver transplantation. Measurement of IL-6 in the bile has been reported to be a useful tool for diagnosing acute rejection of the grafted liver[16–18]. These results suggest that IL-6 in the bile might be a useful parameter for the assessment of liver function after hepatectomy. In the present study, IL-6 concentration was measured in the bile of patients who underwent major hepatectomy, in an effort to determine whether or not it is a useful indicator of postoperative liver function.

Patients and methods

This study involved 24 patients with biliary tract carcinoma who underwent major hepatectomy between October 1995 and July 1997 at this hospital. The study group consisted of 12 men and 12 women with a mean age of 65 (range 44–78) years. Of these, 18 patients had hilar cholangiocarcinoma and six had advanced gallbladder carcinoma. No patient had cirrhosis, but 22 (91·7 per cent) were jaundiced. The jaundiced patients underwent percutaneous transhepatic biliary drainage (PTBD) before operation to relieve the cholestasis and prevent cholangitis[19]. The remaining two patients without jaundice also underwent PTBD in order to evaluate the biliary system precisely[20,21].

The operative procedures performed included right hepatectomy with caudate lobectomy ($n = 15$), extended left hepatectomy with caudate lobectomy ($n = 3$) and extended right hepatectomy with caudate lobectomy ($n = 6$). All patients underwent extrahepatic bile duct resection with biliary reconstruction and extended lymph node clearance[22–24]. A hepatopancreatoduodenectomy was performed in eight patients[25]. Portal vein resection and reconstruction was carried out in two patients[26]. The mean(s.e.) operating time was 777(29) min and operative blood loss was 3724(446) ml. Biliary drainage tubes were placed in all patients during and following surgery. The total number of the tubes placed was 48 (two per patient); 22 were placed via the PTBD sinus tract and the remaining 26 were brought out through jejunal access loops.

The subjects were divided into two groups on the basis of the presence or absence of liver failure after hepatectomy, which was defined as an increase in serum total bilirubin concentration above 10 mg/dl[27–29]. Liver failure developed in six patients (four with hilar cholangiocarcinoma and two with advanced gallbladder carcinoma). Of the six patients, two died from multiple organ failure and one from intra-abdominal bleeding. The remaining three patients recovered from the liver failure and left hospital in good condition. Eighteen patients without liver failure were discharged from hospital in good condition. There were no significant differences in age, sex, disease, indocyanine green disappearance rate (ICG K), estimated remnant liver volume, operating time, liver ischaemic time expressed as a total time of intermittent pedicle occlusion, intraoperative blood loss or operative procedures between the two groups (*Table 1*).

Serum was obtained 1 day before hepatectomy and on days 1, 2, 3, 4 and 6 after operation. Bile samples were obtained at the same time from biliary drainage tubes. The samples from postoperative day 1 were obtained a mean(s.e.) 8·0(0·5) h after operation. The serum and bile samples were stored at −80 °C until analysis. The serum total bilirubin, serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and CRP concentrations were measured, and the hepaplastin test was carried out using standard laboratory methods. IL-6 concentrations in the bile and serum were measured using a two-step sandwich enzyme immunoassay method with an ELISA kit (R & D Systems, Minneapolis, Minnesota, USA), as detailed previously[30]. To clarify whether bile itself and/or the presence of bacteria in bile have an effect on this assay, bile with or without recombinant human IL-6 (rIL-6) (Genzyme, Cambridge, Massachusetts, USA) was also examined. The total bile IL-6 excretion per day (pg/day) was calculated as follows: bile IL-6 concentration (pg/ml) × total bile volume per day (ml/day).

The estimated remnant liver volume was measured before operation by computed tomographic volumetry, as described previously[31]. This was expressed as the percentage of the remnant liver volume to the total liver volume.

The mean(s.e.) was calculated for continuous data. Statistical analysis was performed using the Wilcoxon test and the Mann–Whitney *U* test as appropriate. Fisher's exact probability test was used for dichotomous data. $P < 0·05$ was considered significant.

Table 1 Clinical characteristics of 24 patients undergoing extensive hepatectomy

	Without liver failure ($n = 18$)	With liver failure ($n = 6$)	P
Age (years)*	64(2)	68(2)	0·115*
Sex ratio (M : F)	8 : 10	4 : 2	0·637†
ICG K (min^{-1})*	0·17(0·02)	0·15(0·02)	0·461*
Estimated remnant liver volume (%)*	42(5)	39(2)	0·229*
Surgical procedure			
Extended right hepatectomy + S1	5	1	
Extended left hepatectomy + S1	3	0	
Right hepatectomy + S1†	10 (6)	5 (2)	
Operating time (min)*	784(32)	757(65)	0·571*
Liver ischaemic time (min)*	60(5)	56(6)	0·641*
Blood loss (g)*	3642(555)	3970(201)	0·424*

*Values are mean(s.e.), †values in parentheses indicate the number of patients with combined pancreatoduodenectomy ICG K, plasma disappearance of indocyanine green; S1, caudate lobectomy. *Mann–Whitney *U* test; †Fisher's exact test

Results

Effects of bile on the assay

IL-6 concentrations obtained from bile samples without dilution were low. When bile samples were diluted twofold or more, the data were not affected irrespective of the presence or absence of rIL-6. Furthermore, the presence of bacteria in bile did not have any effect on the results. In this connection, a positive bile culture was found in 16 of the 18 patients without liver failure and in five of the six patients with liver failure (P not significant).

Changes in bile interleukin 6 concentration after hepatectomy

In the 18 patients without liver failure after hepatectomy, the bile IL-6 concentration was significantly increased on day 1 after operation from 56(13) to 2071(398) pg/ml. It remained significantly raised until day 3, decreasing to preoperative values on days 4–6 after operation. In the six patients with postoperative liver failure, the bile IL-6 concentration was significantly increased on postoperative day 1 from 71(24) to 530(76) pg/ml. The bile IL-6 concentration on day 1 after operation was significantly lower in patients with liver failure than in those without (*Fig. 1*).

Changes in serum interleukin 6 concentration after hepatectomy

In the 18 patients without liver failure after hepatectomy, the serum IL-6 concentration was significantly increased on day 1 after operation from 11(2) to 931(178) pg/ml. The serum IL-6 concentrations on days 1–4 after operation were significantly higher than the preoperative values. In the six patients with liver failure, the serum IL-6 concentration was also significantly increased on day 1 after operation from 29(16) to 865(93) pg/ml. The concentrations on days 1 and 2 after operation were significantly higher than the preoperative values. However, no significant differences were observed in serum IL-6 concentration between the two groups (*Fig. 2*).

Changes in the total bile interleukin 6 excretion after hepatectomy

Total bile volume per day before and after hepatectomy did not differ between the two groups (*Table 2*). In the 18 patients without liver failure, the total bile IL-6 excretion was significantly increased on day 1 after operation from 33(11) to 94(20) ng. This returned to preoperative values on day 2. On the contrary, in the six patients with liver failure after hepatectomy, the total bile IL-6 excretion was decreased after hepatectomy. The total bile IL-6 excretion on day 1 after operation was significantly lower in patients with liver failure than in those without (*Fig. 3*).

Serum total bilirubin and interleukin 6 concentrations after hepatectomy

The peak serum total bilirubin concentration after hepatectomy was inversely related to the bile IL-6 concentration on day 1 after operation (*Fig. 4*). Twelve patients who had bile IL-6 concentrations greater than 1000 pg/ml did not develop liver failure after surgery. Six of the remaining 12 patients who had bile IL-6 concentrations

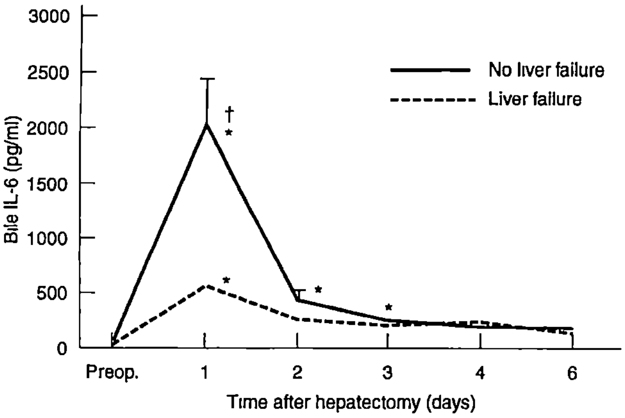

Fig. 1 Mean(s.e.) bile interleukin (IL) 6 concentrations after hepatectomy in patients with ($n = 6$) and without ($n = 18$) liver failure. *$P < 0.05$ *versus* preoperative values; †$P < 0.05$ *versus* patients with liver failure (Mann–Whitney U test)

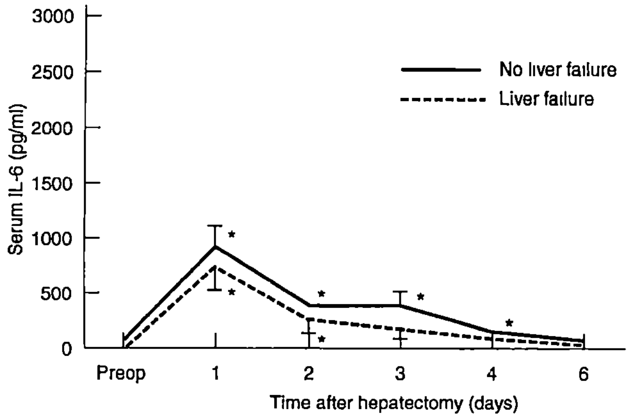

Fig. 2 Mean(s.e.) serum interleukin (IL) 6 concentrations after hepatectomy in patients with ($n = 6$) and without ($n = 18$) liver failure. *$P < 0.05$ *versus* preoperative values (Wilcoxon test)

Table 2 Total bile volume per day before and after hepatectomy

	Total bile volume (ml)		
	Without liver failure ($n = 18$)	With liver failure ($n = 6$)	P*
Before operation	529(80)	618(103)	0·571
After operation			
1	48(7)	35(5)	0·071
2	75(10)	79(28)	0·726
3	80(13)	81(25)	0·861
4	87(24)	117(51)	0·511
6	122(26)	151(58)	0·966

Values are mean(s.e.). *Mann–Whitney U test

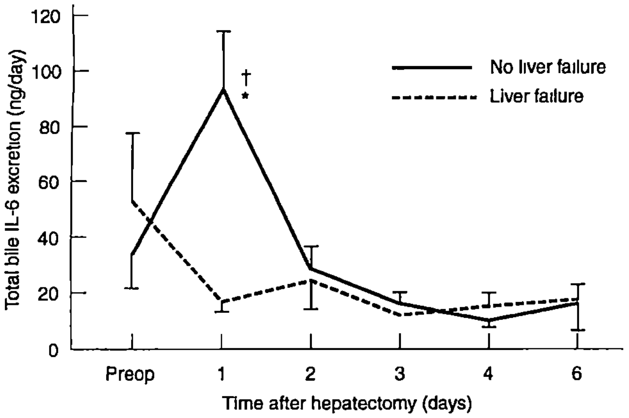

Fig. 3 Mean(s.e.) changes in total bile interleukin (IL) 6 excretion after hepatectomy in patients with ($n = 6$) and without ($n = 18$) liver failure. *$P < 0·05$ *versus* preoperative value (Wilcoxon test); †$P < 0·05$ *versus* patients with liver failure (Mann–Whitney U test)

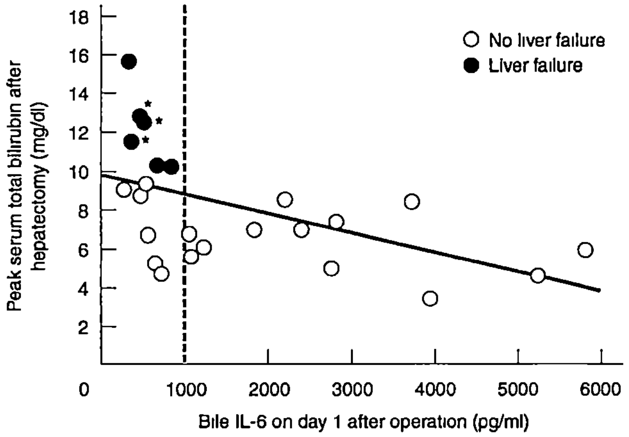

Fig. 4 Correlation between peak serum total bilirubin concentrations and bile interleukin (IL) 6 concentrations on day 1 after hepatectomy ($r = 0·525$, $P = 0·0084$, Pearson's correlation). ○, Patients without liver failure ($n = 18$), ●, patients with liver failure ($n = 6$). *Patients who died

less than 1000 pg/ml had liver failure after hepatectomy. Of these, three died ($P = 0·0137$). The total bile IL-6 excretion on day 1 after operation was also inversely related to the peak serum total bilirubin concentration after operation ($r = 0·592, P = 0·0023$). The 15 patients who had a total bile IL-6 excretion exceeding 25 ng/day did not develop liver failure after operation. However, six of the remaining nine patients who had a total bile IL-6 excretion less than 25 ng/day had liver failure ($P = 0·0006$).

The peak serum total bilirubin concentration did not correlate with the estimated remnant liver volume, the operating time, blood loss during surgery, ICG K, preoperative and postoperative concentrations of serum albumin, AST, ALT, ALP or CRP, or the hepaplastin test. The serum IL-6 concentration on day 1 after operation did not correlate with the peak serum total bilirubin concentration. The bile IL-6 concentration on day 1 after operation did not correlate with the serum IL-6 concentration on the same day, blood loss, operating time, estimated remnant liver volume, ICG K, the concentrations of serum albumin, AST, ALT, ALP or CRP, or the hepaplastin test before and after surgery.

Discussion

IL-6 is a pluripotential cytokine which is a major signal for the stimulation of acute-phase protein synthesis by hepatocytes as a part of the overall inflammatory response[10]. Serum IL-6 levels rise in response to elective surgery such as cholecystectomy and hepatectomy[14,15], as well as sepsis[32] and inflammation[33]. High serum levels of IL-6 have been implicated in postoperative complications including liver failure[15,34]. Maruyama *et al.*[35] have reported a close positive correlation between peak serum IL-6 concentrations and surgical stress, expressed as the operating time and blood loss, in patients with cirrhosis after hepatectomy. Although it was noted in the present study that serum IL-6 concentrations were markedly increased after hepatobiliary resection, there was no significant difference between the levels in patients with or without liver failure. In addition, no correlation was found between the serum level of IL-6 and the surgical stress (blood loss and operating time). The peak serum values observed in the present study were higher than those previously reported for other types of hepatic surgery[14,15,35]. This may indicate higher surgical stress during extensive hepatobiliary resection with biliary reconstruction compared with standard hepatectomy for hepatocellular carcinoma or metastatic liver tumours.

In contrast to serum IL-6 concentrations, little is known about bile IL-6 levels after hepatic surgery. In this study, IL-6 concentrations were higher in bile samples obtained through PTBD catheters before operation and biliary decompression drainage tubes after operation than in corresponding serum samples. The biliary IL-6 concentrations in this series were higher than those in patients who had undergone liver transplantation[16–18]. This might be explained by differences in the operative procedures.

IL-6 is produced in non-parenchymal liver cells, such as Kupffer cells, macrophages and sinusoidal endothelial cells[5,6,8]. Matsumoto *et al.*[36] have reported that IL-6 is produced by biliary epithelial cells, suggesting the possibility of direct excretion of IL-6 into the bile. Tono *et al.*[37] showed no increase in bile IL-6 levels after cardiac transplantation in rats, indicating that the increase in bile IL-6 levels is peculiar to liver surgery and that biliary IL-6 concentration reflects the local condition of the liver. The mechanism of biliary excretion of IL-6 and its biological significance are still poorly understood and need further examination.

In the present study, it was clearly demonstrated that the postoperative peak serum total bilirubin concentration inversely relates to both the bile IL-6 concentration and the total bile IL-6 excretion on day 1 after operation. These observations were not expected, because several authors have stressed that increased serum IL-6 levels are related to the inflammatory response and postoperative complications[10,15,33–35]. Umeshita *et al.*[18] have demonstrated that bile IL-6 concentrations increase immediately after liver transplantation, decreasing to preoperative levels within 48 h, and rising again during acute graft rejection. They concluded that the inflammatory response caused by acute rejection stimulated the excretion of IL-6 in bile, and that the measurement of bile IL-6 was a useful tool for diagnosing acute graft rejection[16–18,37]. However, they did not refer to the relationship between the initial-phase increase in bile IL-6 concentrations and liver function in the graft after transplantation. Recently, IL-6 has been proven to be one of the important components of the early signalling pathways leading to liver regeneration[11–13]. Cressman *et al.*[11] have reported a significantly high incidence of liver failure and suppressed hepatocyte regeneration in IL-6-deficient mice. In the present series, patients with liver failure after hepatectomy had significantly lowered bile IL-6 levels. This appears to imply the impaired biosynthesis of IL-6 as an initial signal for liver regeneration in such patients, which results in liver failure or impaired liver regeneration, in turn. IL-6 detected in the early stages after hepatectomy may reflect the regenerative capacity of the liver. In addition, bile IL-6, rather than blood IL-6, seems to reflect the local response within the liver.

Bile IL-6 concentration on day 1 after operation is a useful parameter for assessing the functional capacity of the remaining liver in the early stages after extensive hepatobiliary resection. This information is useful for postoperative management, especially for salvage treatment such as prostaglandin[38,39] or *N*-acetylcysteine[40,41] administration. However, further studies, including several kinds of liver resection for hepatobiliary diseases, are required to evaluate whether measurement of bile IL-6 is clinically applicable or not.

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Council of The British Journal of Surgery Society is pleased to announce the availability of two European Surgical Fellowships for 1999. Each Fellowship will have a value of up to £3000 and is intended to allow surgeons working in the UK to visit centres in other European countries, or surgeons working in other European countries to visit the UK. Applicants must be under 40 years of age and should submit details of their proposed itinerary, its anticipated cost, a copy of their curriculum vitae and two letters of support from senior colleagues. They should explain briefly how such a visit might broaden their experience and assist their career. Fellowships will not be awarded solely for the purpose of attending courses or meetings.

Applications should be sent to Mr J. R. C. Sainsbury, Company Secretary, The British Journal of Surgery Society, Department of Surgery, The Royal Infirmary, Lindley, Huddersfield HD3 3EA, UK by 31 May 1999.

J. R. C. Sainsbury

Incidence, aetiology and mortality rate of acute pancreatitis over 10 years in a defined urban population in Sweden

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Background: There is a wide range (5–50 per 100 000) in the reported annual incidence of acute pancreatitis. Furthermore, the predominant aetiology varies in different reports. This study was undertaken to establish the current incidence, aetiology and associated mortality rate in a defined population.
Methods: A retrospective study of all cases of acute pancreatitis admitted over a 10-year period to a single institution was performed. In addition the autopsy and forensic materials were reviewed.
Results: Altogether 883 attacks of acute pancreatitis were recorded, of which 547 were first attacks. The annual incidence of first attacks was 23·4 per 100 000. Including relapses, the incidence was 38 2 per 100 000. Biliary disease was the main aetiological factor in first attacks whereas alcohol was the predominant factor when relapses were included. The mean annual mortality rate for acute pancreatitis in the population was 1·3 per 100 000. Of 31 patients who died from acute pancreatitis only 15 were diagnosed before death. For recurrent disease the mortality rate was 0·3 per cent. In 12 patients the pancreatitis was associated with pancreatic carcinoma.
Conclusion: It is important to differentiate between first attacks and relapses, since both incidence and aetiology figures are influenced by this, and it is important to include autopsy and forensic material in population-based mortality studies.

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Introduction

The annual incidence of acute pancreatitis in different reports ranges from 5 to 50 per 100 000[1–12]. This divergence may in part be due to differences in alcohol consumption or in the incidence of gallstone disease in different parts of the world. Patient selection, referral of patients and missed diagnosis can also explain the differences to some extent. In Finland the incidence of acute pancreatitis is high, especially in men. Here, and in reports from Sweden[11] and Amsterdam[14], alcohol is the most common aetiology. Gallstone disease has been reported to be the most common cause in reports from England[1,2,4,5,15,16], Scotland[3,17], and recently from Norway[12] and Germany[18]. A number of reports suggest an increasing incidence of acute pancreatitis[1,2,4,7,10]. Whether this is a true rise or, in some cases, just a sign of greater accuracy in diagnosis, is difficult to say. Alcohol as an aetiological factor of rising importance has also been suggested[4,8,11,13].

Mortality rates vary between 2 and 22 per cent[1–4,7,8,10–20]. These figures are often difficult to compare since the mortality rate is seldom related to a defined population but rather to the number of cases of acute pancreatitis treated at a specific hospital. Most series of acute pancreatitis described are selected populations at referral centres. Few studies have been carried out recently to establish the epidemiology of acute pancreatitis in a defined population.

Malmö is the third largest city in Sweden. During the study period the population increased from 229 107 in 1985 to 240 073 in 1994. There is only one hospital for somatic disease so all patients in the population needing treatment for acute abdominal disorders, such as acute pancreatitis, are admitted to this hospital. There are no referrals of patients with acute pancreatitis to or from other hospitals.

The present study is a retrospective survey of acute pancreatitis in Malmö, covering 10 years from 1985 to 1994. The study was undertaken to establish the current incidence, aetiology and mortality rate of acute pancreatitis in a defined population.

Patients and methods

Diagnostic criteria

Patients were identified from hospital records, with the aid of a computer search (International Classification of Diseases 577A). All records were reviewed and the diagnosis of acute pancreatitis was only accepted in those with a consistent clinical history and physical examination, supported by an increase in serum amylase level. Evidence from laparotomy, laparoscopy or necropsy was also accepted for the diagnosis. The autopsy records at the Department of Pathology were reviewed. The autopsy rate in the population during the study period was 42 per cent. In addition a search was made in the death certificate records at the Coroner's Office, to identify individuals dying from acute pancreatitis outside hospital, and these patients' records were reviewed.

Aetiology

Alcohol

Alcohol was considered the aetiology when the patient reported a regular high intake of alcohol or an alcoholic bout directly before the onset of the disease, and no signs of other aetiologies, such as gallstone disease, were present.

Biliary disease

Ultrasonography for gallstone disease was routinely performed in most patients early in the course of the disease. In a minority of cases oral cholecystography or endoscopic retrograde cholangiopancreatography (ERCP) was performed. Biliary disease was considered the aetiology when there were positive findings of gallstones and no signs of alcohol abuse or other aetiology.

Unknown

The aetiology was considered to be unknown when no aetiological factor could be found, or when the patient had signs of both alcohol abuse and gallstone disease.

Results

Incidence

Altogether 883 episodes of acute pancreatitis were identified, in 587 patients. Five hundred and forty-seven were first attacks, and the mean annual incidence of first attacks was 23·4 per 100 000. Of these patients 58·1 per cent were men and 41·9 per cent were women, giving an incidence of first attacks in men of 28·7 per 100 000 per year, and in women of 18·7 per 100 000 per year. A comparison of the last 5 years with the first five is shown in *Table 1*. With episodes of relapse included and all discharges from hospital considered, the mean annual incidence was 38·2 per 100 000 (men 51·0 per 100 000 and women 26·0 per 100 000).

Aetiology

Including both men and women with first attacks, gallstones were the most common aetiology, representing 38·4 per cent of cases, followed by alcohol, 31·8 per cent; unknown, 23·2 per cent; miscellaneous, 2·7 per cent; ERCP, 2·4 per cent and pancreatic carcinoma, 1·5 per cent. The aetiologies according to sex are shown in *Fig. 1*.

The age distribution for first attacks of gallstone-induced and alcohol-related acute pancreatitis is shown in *Fig. 2*, together with that for pancreatitis of unknown

Table 1 Incidence of first attacks of acute pancreatitis in men and women during the first and second 5-year period of the study, according to aetiology

	Men		Women	
	1985–1989	1990–1994	1985–1989	1990–1994
Alcohol	13·5	12·3	3·0	2·1
Gallstones	6·2	8·4	9·4	11·6
Unknown	6·2	6·9	4·5	4·5
Miscellaneous	0·7	0·4	0·3	1·0
ERCP	0·6	0·9	0·7	0·2
Pancreatic carcinoma	0·6	0·7	0	0·2
Total	27·8	29·6	17·8	19·6

Values are incidence per 100 000 per year. ERCP, endoscopic retrograde cholangiopancreatography

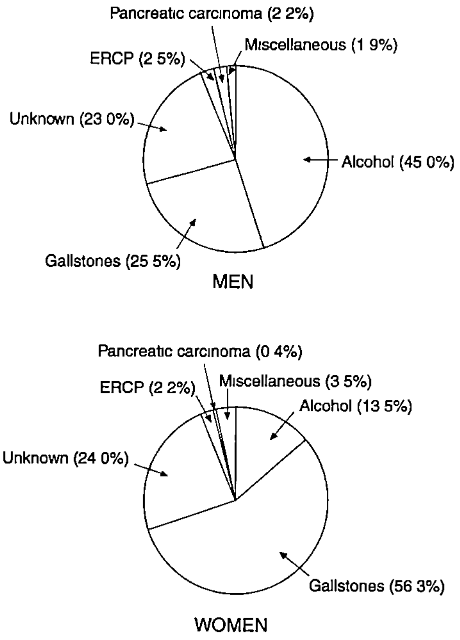

Fig. 1 Aetiology of first attacks of acute pancreatitis in men and women. ERCP, endoscopic retrograde cholangiopancreatography

aetiology. Fifteen patients had unusual (miscellaneous) aetiologies (*Table 2*).

With recurrent attacks included alcohol was the most common aetiology, representing 43·3 per cent of cases, followed by gallstones, 31·5 per cent; unknown, 21·2 per cent; miscellaneous, 1·7 per cent; ERCP, 1·5 per cent and pancreatic carcinoma, 0·9 per cent.

Table 2 Miscellaneous aetiologies of acute pancreatitis

Aetiology	No. of patients
Postoperative	6
Hyperlipidaemia	2
Duodenal diverticula	2
Coxsackie virus	1
Epstein–Barr virus	1
Diabetes	1
Bile duct anomaly	1
Acetic acid	1
Total	15

Recurrence

During the study period 154 patients were readmitted with 336 relapses. Relapsing pancreatitis was most commonly related to alcohol (*Table 3*). The risk of at least one relapse after a first attack of acute pancreatitis, within the 10-year period is shown, according to aetiology, in *Table 4*.

Endoscopic retrograde cholangiopancreatography

During the study period 1855 ERCP examinations were performed. Of these 730 (39·4 per cent) were diagnostic and 1125 (60·6 per cent) were therapeutic. Thirteen episodes of ERCP-induced acute pancreatitis were identified, giving an incidence of 0·7 per cent. Two of these patients

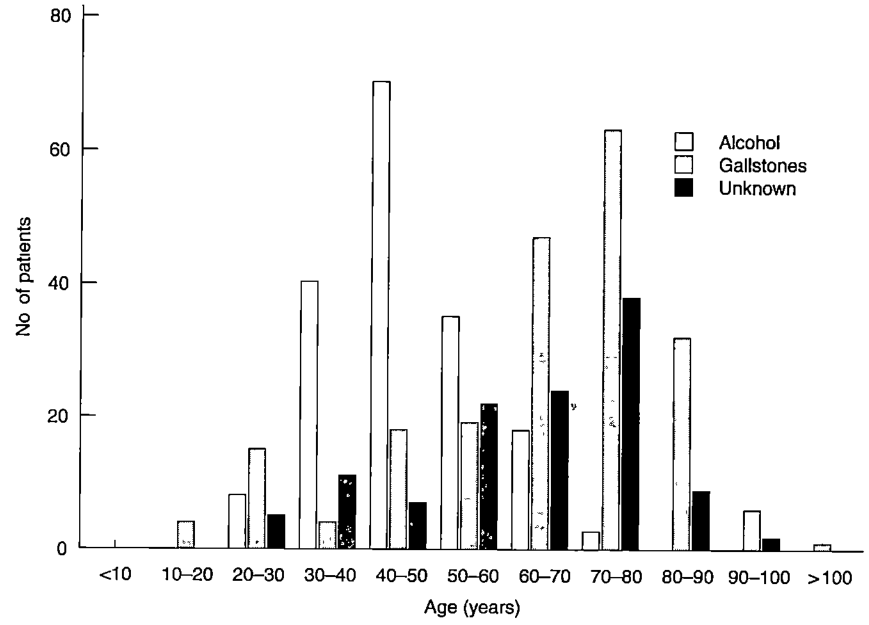

Fig. 2 Age distribution of patients with a first attack of acute pancreatitis

Table 3 Aetiology of recurrent acute pancreatitis

Aetiology	Men (%)	Women (%)	Total (%)
Alcohol	67·8	44·0	61·3
Gallstones	13·9	36·3	19·9
Unknown	16·7	19·8	17·6
Other	1·6	0	1·2

Results are presented as a percentage of all recurrent cases in each group

Table 4 Risk of relapse

Aetiology	Risk (%)
Alcohol	48·3
Gallstones	21·0
Unknown	18·7
Other	5·7
Total	28·2

Values are percentage risk of relapse after a first attack of acute pancreatitis (no. of patients with at least one relapse/total no. of first attacks × 100)

died, giving a 0·1 per cent risk of dying from acute pancreatitis after ERCP.

Pancreatic carcinoma

Twelve episodes of acute pancreatitis were associated with pancreatic carcinoma. In eight of these patients it is reasonable to assume that the aetiology of the attack was the cancer, as these patients had the pancreatic cancer diagnosed within 3 years of the first attack. In the other four instances, more than 3 years had elapsed since the first attack of acute pancreatitis, before the cancer was diagnosed. Three of these four patients had recurrent episodes of alcohol-induced acute pancreatitis.

Deaths

Altogether 31 patients died from acute pancreatitis, giving a mortality rate of 1·3 per 100 000 per year. Of these, ten were identified from the forensic material and never admitted to hospital (*Table 5*). Of the 21 patients dying from acute pancreatitis in hospital (mortality rate 2·4 per cent) six were not diagnosed until autopsy. Only one of the deaths was caused by recurrent pancreatitis. There were no deaths from 206 relapses of alcohol-induced disease.

The aetiology and sex distribution for the fatal cases are shown in *Table 5*, together with the mortality rate for each group. The median age of patients who died was 69 (range 48–92) years, compared with a median of 59 (range 15–101) years for all patients with a first attack.

Table 5 Sex distribution and aetiology in fatal cases

	Patient material		
	Clinical	Forensic	Total
Men	15	6	21 (3·7)
Women	6	4	10 (3·1)
Alcohol	2	6	8 (2·2)
Gallstone	6	1	7 (2·5)
Unknown	10	2	12 (6·3)
ERCP	2	0	2 (15)
Postoperative	1	0	1
Acetic acid	0	1	1

Values in parentheses are percentage of all cases (including relapses) in each group. ERCP, endoscopic retrograde cholangiopancreatography

Discussion

Comparing the incidences of acute pancreatitis between different reports is difficult. Few studies report the incidence of first attacks of acute pancreatitis in a defined population, since first attacks are difficult to identify in large, retrospective, epidemiological studies in which the individual patient records are not reviewed. This study is derived from a single institution serving the whole population of one city, with no extramural referrals. The incidence found in this study is similar to that reported from other centres in Scandinavia[9] and Germany[8] but significantly higher than that reported from the UK. Studies from the UK reporting the incidence of first attacks are from the 1970s, and suggest incidences of 5·4–9·4 per 100 000 per year[1–6]. A later report from Scotland describes an increasing incidence of all discharges from hospital (11-fold) between 1961 and 1985 with an annual incidence of 23·3 per 100 000 during the last 5 years[7]. The low incidences reported from many centres in the UK are true 'first attack incidences'. The inclusion of recurrent attacks results in substantially higher incidences, in the present material more than 50 per cent higher. This effect is potentiated if the material contains a large proportion of alcohol-induced episodes, since the recurrent attacks usually fall within this category. This sheds some light on the high annual incidences reported in Finnish[10] and Swedish[11] studies (50 per 100 000 and 40 per 100 000 inhabitants older than 15 years respectively), since these studies include all cases and also report a high proportion of alcohol-induced disease. This may to some extent also explain the low figures from some English and Scottish centres, since these centres report a high proportion of biliary pancreatitis.

Aetiology figures are also influenced by whether recurrent disease is included or not. In this survey, looking only at first attacks, gallstones were the main aetiology, but alcohol was the predominant cause when relapses were included. Older studies from the UK regularly report a low fraction of alcohol-related disease (less than 21 per cent). Here gallstones were the predominant factor, representing 40–60 per cent of cases[1–5,15,17,19]. In a more recent study from London (1988–1992), however, alcohol represented 29 per cent and gallstones 30 per cent of episodes[16]. Older studies from Germany[8], Finland[13] and Sweden[11] have shown a shift in predominant aetiology from gallstones to alcohol. In recent studies from Germany[18] and Norway[12], however, gallstones were clearly predominant.

Most studies are retrospective. It is therefore interesting to note that a recent, small, Norwegian prospective study finds a high incidence, 42 per 100 000 per year (including relapses), combined with a high proportion of gallstone-induced acute pancreatitis[12].

In this study there seems to be a small increase (less than 10 per cent) in the incidence of first attacks when the two 5-year periods are compared. For both men and women this increase is the result of an increase in gallstone-induced disease. This in turn may be explained by an increased proportion of older people in the population studied.

Sixteen attacks of acute pancreatitis were not detected until autopsy, and it is therefore likely that many patients with mild attacks of acute pancreatitis are never diagnosed. Although the incidence of acute pancreatitis in this study is fairly high, it can be assumed that the true incidence is even higher.

Many studies reporting low incidences also report high mortality rates, as a percentage of the total number of episodes treated. One explanation for a low incidence could be that few mild cases are included. This is probably true for some older surveys where the diagnosis was missed more often, and for material from large referral hospitals.

Missed diagnosis is a well known problem[21,22]. Of 31 patients in the present review who died from acute pancreatitis only 15 were diagnosed before death. Most surprising was that as many as ten episodes were identified in forensic material, from patients never admitted to the hospital.

Mortality rates for hospitalized patients with acute pancreatitis vary enormously (2–22 per cent)[1–4,7,8,10–20]. Mortality figures in population-based studies show much less variation. The mortality rate from acute pancreatitis in this study was 1·3 per 100 000 per year. The nationwide study from Finland published in 1993[10] revealed, along with an increasing incidence, a decreasing mortality rate, from 2·9 per 100 000 in 1970 to 1·8 per 100 000 in 1989. In Scotland[7] the mortality rate was 1·3 per 100 000 per year between 1981 and 1985. Studies from centres in the UK in the 1970s show mortality figures ranging between 0·9 and 1·6 per 100 000 per year[1–4].

After ERCP most patients develop hyperamylasaemia and it is not unusual for patients to complain of transient abdominal pain, from which they recover within 24 h[23]. These mild cases are not included in the present study and may explain the high mortality rate (15 per cent) in this category. The 0·1 per cent risk of dying from acute pancreatitis after ERCP seen in this study is, however, in accordance with that found at other centres[4,24–26].

In this study there was only one fatal case in 336 relapses. As in previous reports[2,3,11] it appears that recurrent attacks of acute pancreatitis represent a relatively benign condition, with a low associated mortality rate. Some investigators, however, have found a high mortality rate even for recurrent disease[4].

This series included 12 patients with pancreatic carcinoma. Considering the crude incidence of pancreatic carcinoma in the Malmö population, 18·1 per 100 000 per year, only one episode should be expected if there was no relationship between the diseases[27]. In the individual case it is impossible to firmly establish which disease caused the other. The attack of acute pancreatitis probably was the first symptom of the pancreatic tumour in eight patients and the development of the cancer was probably secondary to the pancreatitis in four, as described previously[28–30]. These figures are very similar to findings in Bristol[2] and North-East Scotland[21].

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Estimation of mortality and morbidity risk in vascular surgery using POSSUM and the Portsmouth predictor equation

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Background: The Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) is a simple scoring system previously validated in general surgical patients which enables estimation of the risk of complications and death after operation. The Portsmouth predictor equation (P-POSSUM) is a modification that may result in more accurate prediction of death than POSSUM. The aim of this study was to test the validity of POSSUM and P-POSSUM in patients undergoing major arterial surgery in a specialist unit.

Methods: Physiological and operative severity scores in 221 patients undergoing elective and emergency arterial surgery in a pure vascular practice under a single consultant were recorded prospectively. Observed morbidity and mortality rates were compared with the rates predicted by POSSUM and P-POSSUM using a linear method of analysis.

Results: The POSSUM equation overestimated deaths with this analysis but the mortality rate estimated by P-POSSUM was not significantly different from the observed death rate. The risk of morbidity predicted by POSSUM was not significantly different from the observed complication rate.

Conclusion: The POSSUM methodology combined with the P-POSSUM adjustment for death allows satisfactory prediction of mortality and morbidity rates in patients undergoing vascular surgery.

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Introduction

League tables with comparisons between different surgical units and individual surgeons may be adopted, especially as the efficacy of self-regulation is being questioned. A critical appraisal of the methodology for such comparisons is required. It has been well demonstrated that comparisons using crude mortality and morbidity data are misleading and lead to erroneous conclusions[1–3]. True comparisons can only be made if risk adjustment is used to allow for the differences in case mix between different units and surgeons.

The Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) provides a possible tool for risk adjustment and comparative audit. POSSUM was developed from a multivariate discriminant analysis of factors measured in a broad group of general surgical patients[4]. Using commonly recorded parameters the system determines a physiological score and an operative severity score from which expected morbidity and mortality rates can be calculated using logistic regression equations. Specialized or unusual measurements are not required unlike many other scoring systems.

A revised equation for deaths has been proposed called the Portsmouth predictor equation (P-POSSUM). This followed a study in which the POSSUM mortality predictor equation was found to overpredict death in general surgical patients, especially in low-risk patients[5]. P-POSSUM was developed in a unit separate from that which developed POSSUM but used the same physiological and operative scores. Wijesinghe *et al.*[6] compared POSSUM and P-POSSUM in predicting death following vascular surgery, and demonstrated good agreement between the observed and predicted number of deaths providing the correct analysis was performed. They observed a better prediction of death with P-POSSUM than POSSUM when the simpler 'linear' analysis was used. However, this study made no attempt to analyse morbidity.

Predicting morbidity using POSSUM has been evaluated less extensively than death because of difficulties associated with definitions and collection of accurate data relating to complications. Morbidity is an important endpoint for assessing surgical performance and has implications for both a patient's quality of life as well as consumption of health care resources. A valid comparison of morbidity between units would be valuable.

The aim of this study was to examine prospectively the value of POSSUM and P-POSSUM in predicting both mortality and morbidity rates in a purely vascular surgical practice.

Patients and methods

Two hundred and twenty-one patients admitted under a single consultant vascular surgeon (S.A.) for either emergency or elective surgery had their POSSUM physiological score recorded prospectively. This was performed within the 24 h preceding the operation. Immediately after operation the surgeon completed a scoring sheet to record the operative severity score. Complications were recorded and defined as in the original paper describing the development of POSSUM[4] except that graft thrombosis was added as a specific complication. Complications and death within 30 days of the operation were recorded on a prospective basis.

A 'linear' type of analysis was performed. The mean predicted risk for patients in each risk grouping was calculated and multiplied by the number of patients in the group to give the predicted number of patients. The predicted mortality and morbidity rates were subsequently compared with the observed rates, using χ^2 analysis to determine if the differences were statistically significant.

Results

The overall mortality and morbidity rates were 6·3 and 57·9 per cent respectively. The operative procedures performed and the types of complication are shown in *Tables 1* and *2* respectively.

The POSSUM predicted and observed morbidity rates for different risk groupings are shown in *Table 3*. The difference between the observed and predicted morbidity was not significant (χ^2 = 14·5, 9 d.f., P = 0·11). The POSSUM logistic equation for morbidity accurately predicted the risk of a postoperative complication developing in this group of vascular patients.

The number of deaths predicted by POSSUM and P-POSSUM and the observed number of deaths for different predicted risk groupings are shown in *Tables 4* and *5* respectively. The mortality rate predicted by POSSUM was significantly higher (χ^2 = 24·04, 6 d.f., $P < 0·001$) than the observed rate. The mortality rate predicted by P-POSSUM was not significantly different from the observed rate (χ^2 = 9·00, 6 d.f., P = 0·17).

Table 1 Type of operation

Operation type	No.
Lower limb graft (PTFE)	56
Lower limb graft (vein)	48
Lower limb extra-anatomic bypass	18
Abdominal aorta (elective)	43
Abdominal aorta (emergency)	13
Thoracoabdominal aneurysm	3
Carotid endarterectomy	14
Embolectomy/exploration	20
Revision grafts	7
Other	16

Multiple procedures are counted separately. PTFE, polytetrafluoroethylene

Table 2 Complications

Complication	No.
None	93
Haemorrhage	
Wound	6
Deep	8
Other	1
Infection	
Chest	17
Wound	15
Urinary tract	4
Deep	0
Septicaemia	1
Other	1
Wound dehiscence	
Superficial	7
Deep	0
Anastomotic leak	0
Thrombosis (non-graft)	
Deep vein thrombosis	0
Pulmonary embolus	1
Cerebrovascular	1
Myocardial infarction	2
Thrombosis (graft)	7
Cardiac failure	7
Impaired renal function*	9
Hypotension†	6
Respiratory failure	6
Other complication	17
Death	14

Multiple complications are counted separately. *Urea increase greater than 5 mmol/l above preoperative value. †Less than 90 mmHg for more than 2 h

Examination of the observed : predicted ratios showed that both POSSUM and P-POSSUM ratios for death were less than 1 for all risk groupings except the 90–100 per cent group, indicating an overestimation of mortality risk in all risk groups except the highest. The departure from unity of the observed : predicted ratio was less in all groups for P-POSSUM than POSSUM except for the 20–

Table 3 Comparison of observed morbidity and predicted morbidity from POSSUM logistic regression

Risk of morbidity	No. of operations	Mean risk	No. of patients with complications		Observed : predicted ratio
			Predicted*	Observed	
> 0 ≤ 20	35	14·2	5	11	2·2
> 20 ≤ 30	27	26·2	7	10	1·4
> 30 ≤ 40	30	34·8	10	14	1·4
> 40 ≤ 50	22	45·5	10	14	1·4
> 50 ≤ 60	23	54·9	13	16	1·2
> 60 ≤ 70	21	63·6	13	11	0·8
> 70 ≤ 80	13	76·2	10	10	1·0
> 80 ≤ 90	23	86·4	20	14	0·7
> 90 ≤ 100	27	94·7	26	26	1·0

*Rounded to nearest whole number

Table 4 Comparison of observed and predicted deaths from POSSUM logistic regression equation

Risk of death	No. of operations	Mean risk	No. of deaths		Observed : predicted ratio
			Predicted*	Observed	
> 0 ≤ 10	114	5·4	6	1	0·17
> 10 ≤ 20	45	13·6	6	1	0·17
> 20 ≤ 40	31	29·8	9	2	0·22
> 40 ≤ 70	16	52·7	9	1	0·11
> 70 ≤ 90	9	80·6	8	3	0·38
> 90 ≤ 100	6	94·5	6	6	1·00

*Rounded to nearest whole number

40 per cent group, indicating that P-POSSUM overestimated deaths to a lesser extent overall. For the POSSUM morbidity equation, the observed : predicted ratio showed no consistent deviation from 1 across the risk groupings.

Discussion

Comparisons between surgical units or individual surgeons must take into account differences in patient populations and the complexity of surgery performed in order to be meaningful and reliable. When risk estimation is used to facilitate patient selection for a given treatment, a disease-specific tool with a high degree of accuracy is required for risk–benefit estimation. POSSUM has provided a useful audit tool for estimating morbidity and mortality risk using commonly measured parameters. POSSUM has been shown to be better than Acute Physiology And Chronic Health Evaluation II[7] for estimating the mortality rate in a high-dependency unit and is simpler to apply. P-POSSUM was developed following reports that POSSUM tended to overestimate the mortality rate[5], particularly in low-risk patients. It should be appreciated that the relative performance of POSSUM and P-POSSUM may depend on the method of analysis[6]. In the 'linear' method the patients are divided into risk groupings according to the predicted risk. The predicted number of deaths in each group is calculated by multiplying the mean risk of the group by the number of patients in the group. The 'exponential' method considers a cut-off risk of death at each stage and divides the patients into those above or below this level, recalculating the number of patients at each cut-off level. The number of predicted deaths at a given risk cut-off is the number of patients with a predicted risk above the cut-off level multiplied by the cut-off being considered. The 'linear' analysis has distinct advantages over the 'exponential' analysis owing to its simplicity and the fact that each patient only contributes to the analysis once.

Using the linear analysis method, P-POSSUM gave a better estimation of mortality rate than POSSUM in vascular surgical patients. Both POSSUM and P-POSSUM overestimated the number of deaths compared with the observed deaths for all risk groups except the highest (90–100 per cent risk) but this difference was not significant with P-POSSUM. The POSSUM morbidity equation satisfactorily estimated the risk of a postoperative complication. It would therefore seem valid to use P-POSSUM mortality and POSSUM morbidity equations to stratify risk in patients undergoing vascular surgery.

Differences between this data set and the POSSUM or P-POSSUM predictions may have occurred for several

Table 5 Comparison of observed and predicted deaths from Portsmouth-POSSUM logistic regression equation

			No. of deaths		
Risk of death	No. of operations	Mean risk	Predicted*	Observed	Observed : predicted ratio
> 0 ≤ 10	163	2·7	4	3	0·75
> 10 ≤ 20	24	15·5	4	1	0·25
> 20 ≤ 40	15	27·1	4	0	0·00
> 40 ≤ 70	6	51·0	4	2	0·50
> 70 ≤ 90	8	81·4	6	3	0·50
> 90 ≤ 100	5	94·2	5	5	1·00

*Rounded to nearest whole number

reasons. First, the parameters used might not be the optimal combination of factors for accurate prediction of death and complications in patients undergoing arterial surgery. Second, it may be that this unit's performance was substantially different from that of the departments in which the equations were developed, particularly with respect to death. Third, the data set may have been too small.

The most satisfactory way to resolve these difficulties would be to collect the POSSUM parameters making up the physiological and operative scores from multiple centres and to perform a logistic regression analysis on these data. By involving multiple units in the development of the equations the problem of local bias would be minimized and the equations may be more generally applicable. Having developed the equations, verification would be required from a new data set from the same units. If a good fit was obtained the equations could be adopted as standards for risk adjustment in comparative audit. Such equations could also be used by an individual surgeon or unit to assess his/her own performance.

Rutherford[8] considered the POSSUM methodology to be the best available for comparing mortality and morbidity rates but suggested that a system should be developed specific to vascular surgery. The parameter 'presence of malignancy' included in the operative score would have an infrequent impact in vascular surgery. However, the strength of the POSSUM method is the broad applicability which allows it to be applied to specialist as well as more general surgical practice.

With pressure to examine surgical performance critically it is vital that the pitfalls of crude mortality and morbidity statistics and the necessity of risk adjustment are understood by anyone wishing to scrutinize surgical outcomes. If clinical indicators are used with no regard for case mix, tertiary referral centres and high-risk patients could be disadvantaged. The POSSUM and P-POSSUM systems have been validated in several general surgical units and, based on this study, appear to work favourably for the subspecialty of vascular surgery.

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Influence of volume of work on the outcome of treatment for patients with colorectal cancer

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Background: Recent recommendations for the reorganization of cancer services emphasize the importance of a 'minimal acceptable volume of work'. The influence of both hospital and surgical workload has been examined using a population-based series of patients with colorectal cancer.

Methods: Nine hundred and twenty-seven patients with primary colorectal cancer diagnosed during the period 1 January to 30 June 1993 were identified from the North Western Regional Cancer Registry. Case notes were reviewed for information on patient age and sex, histological diagnosis, disease stage, degree of tumour differentiation, mode of admission, identity of operating surgeon, timing of operative procedure, and use of radiotherapy and/or chemotherapy. A multivariate Cox proportional hazards model was then constructed to examine, simultaneously, the effects of patient-, disease- and health service-related variables on survival.

Results: Age, tumour stage and differentiation, and mode of admission were revealed as significant independent prognostic variables. After adjusting for these variables, neither operator grade (consultant *versus* junior), consultant workload nor hospital throughput were identified as independently influencing patient survival.

Conclusion: The results of this study do not support an association between volume of work and patient outcome.

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Introduction

Recent recommendations for the reorganization of cancer services advocate the delivery of services by specialist clinicians based in high-volume units[1]. However, the importance of volume of work in influencing outcome from colorectal cancer remains unclear. Hospital-based series have demonstrated substantial intersurgeon variation in outcome from large bowel disease[2–5], but the generalization of these findings is likely to be confounded by differences in case-mix. In the present study, a population-based series of colorectal cancers has been used to identify prognostic variables and to examine the influence of volume of work on survival.

Patients and methods

Subjects

All cases of colorectal cancer (International Classification of Diseases (ICD) version 9 site codes 153, 154 and 159) arising in residents of the North Western region of England during the 6-month period 1 January to 30 June 1993 were identified from records held by the North Western Regional Cancer Registry (NWRCR), and the patients' hospital case notes were requested for review.

Study variables

Information on the following variables was abstracted from hospital case notes: sex, age at diagnosis, histological diagnosis, tumour subsite, disease stage, degree of tumour differentiation, date and mode of admission, operating surgeon, date and nature of operative procedure, and use of radiotherapy and chemotherapy.

Information abstracted from operative records, pathology reports and the results of clinical investigations was used to assign disease stage according to the clinicopathological modification of the Dukes classification system[6]. Tumour subsite was recorded as colon or rectum, with tumours in the rectosigmoid categorized as rectal disease. Treatment centre was defined as the hospital in which the patient underwent the primary operation or, if surgery was not undertaken, the hospital to which they were first admitted. Mode of admission was categorized as either planned (elective) or unplanned (when the patient was admitted from the accident and emergency department or directly from an outpatient clinic). An 'out of hours' procedure was one performed after 17.00 hours but before 08.00 hours and was considered to have been undertaken by a consultant surgeon if a consultant's name appeared on the operation record. For 125 patients (15 per cent) it was not possible to assign confidently the status of the surgeon who undertook the procedure.

When the effect of throughput was examined at the level of the individual surgeon, analyses were based on the consultant responsible for the patient's care rather than the member of the surgical team who performed the operation. The throughput of a hospital was defined in terms of the number of patients in the study population who were admitted for the management of colorectal adenocarcinoma.

When exploring the effect of throughput on outcome measures, an exhaustive set of cut-off points was used to partition the data set into groups with a 'low' and 'high' throughput. The four cut-off points selected for presentation correspond to a recognizable monthly workload undertaken by surgeons and were: one to six procedures during the study period (one or fewer patients with colorectal cancer managed surgically per month); seven to 12 (between one and two per month); 13–18 (between two and three per month); and 19 or more (more than three per month). Four hospital throughput groups were established (30 or less; 31–45; 45–55; and 56 or more admissions); this divided the study population approximately into quartiles.

Indicators of quality of care

Clinical management was assessed in relation to three process measures derived from published guidelines on the management of colorectal cancer produced by the Royal College of Surgeons of England[7]. These were: (1) the proportion of rectal tumours treated by abdominoperineal excision of the rectum (APR); (2) the proportion of patients undergoing 'screening' for liver metastases by means of computed tomography (CT) or ultrasonography; and (3) the proportion of patients operated on 'in hours' by a consultant surgeon having been admitted as an unplanned admission.

Statistical analysis

Frequency distributions were constructed for each variable and compared using χ^2 tests or t tests where appropriate. In tests for linear trend, the score assigned to a group was the mean value for that group. Survival times were measured from the date of operation until death from any cause, with censoring after 30 June 1996. For patients who did not undergo an operation, survival was measured from date of first non-surgical treatment or, where no therapeutic intervention was undertaken, date of diagnosis. Vital status was determined from NWRCR records. Postoperative deaths were defined as those occurring within 30 days of an operative procedure, and included intraoperative deaths.

Survival was estimated for the 3 years following treatment of disease; this was the maximum complete period for which information on status was available for all patients. The influence of study variables on survival was first examined in univariate analyses, using the Kaplan–Meier method and log rank tests of significance. A multivariate Cox proportional hazards model was then constructed to examine, simultaneously, the effects of these variables on survival. All tests of significance were performed at the 5 per cent two-sided level.

Results

One thousand and three patients with colorectal cancer were identified. Seventy-six patients were excluded: 15 first diagnosed at post-mortem examination; seven for whom the only notification of cancer was the death certificate; four with a tumour of the large bowel other than adenocarcinoma; 21 who had no contact with hospital services; and 29 for whom case notes were not available for review. The remaining 927 patients comprise the study population; there were 548 cases of colon cancer (59 per cent) and 379 of cancer of the rectum (41 per cent).

Identification of prognostic variables

Table 1 shows the distribution of study variables and the results of univariate survival analyses: patients who were older, had late stage disease, had poorly differentiated tumours or who had an unplanned admission were significantly more likely to have an adverse outcome. Multivariate analysis revealed these variables to be significant independent prognostic factors (*Table 2*). When survival analyses were restricted to patients who underwent surgery, time of operation and operator status were also identified as prognostic variables in the univariate, but not the multivariate, analyses.

Table 1 Distribution of variables and univariate survival analysis ($n = 927$)

	No of patients	Survival (%) 1 year	2 years	3 years	Median survival (months)	
Site						
Colon	548 (59)	54	44	38	16·5	$\chi^2 = 0·79$, 1 d.f., $P = 0·37$
Rectum	379 (41)	61	47	40	20·8	
Sex						
M	467 (50)	58	47	39	19·8	$\chi^2 = 0·15$, 1 d.f., $P = 0·70$
F	460 (50)	56	44	39	17·5	
Age (years)						
≤59	144 (16)	72	59	52	41·9‡	$\chi^2 = 29·45$, 2 d.f., $P < 0·0001$
60–69	266 (29)	63	53	45	26·6	
≥70	517 (56)	50	37	32	11·9	
Mode of admission*						
Planned	624 (70)	67	55	49	33·2	$\chi^2 = 114·26$, 1 d.f., $P < 0·0001$
Unplanned	271 (30)	35	24	18	5·5	
Stage						
A	111 (12)	87	83	79	41·9‡	$\chi^2 = 401·51$, 4 d.f., $P < 0·0001$
B	281 (30)	78	67	61	41·9‡	
C	206 (22)	69	49	37	22·4	
'D'	187 (20)	20	8	4	3·9	
Unknown	142 (15)	23	18	14	2·8	
Differentiation						
Well	191 (21)	72	62	55	41·9	$\chi^2 = 135·45$, 3 d.f., $P < 0·0001$
Moderate	428 (46)	69	53	46	27·9	
Poor	100 (11)	43	31	26	7·5	
Unknown	208 (22)	26	20	17	3·4	
Time of operation†						
In hours	542 (66)	66	52	45	26·6	$\chi^2 = 6·25$, 2 d.f., $P = 0·0439$
Out of hours	76 (9)	47	42	34	9·5	
Unknown	203 (25)	65	49	44	23·1	
Operator status†						
Consultant	554 (67)	67	55	47	31·3	$\chi^2 = 16·91$, 2 d.f., $P = 0·0002$
Other grade	142 (17)	62	47	42	19·8	
Unknown	125 (15)	51	36	30	13·1	

Values in parentheses are percentages *Thirty-two cases for which mode of admission was unknown have been excluded from analysis, †refers only to the 821 cases managed surgically ‡Censored survival time

Table 2 Multivariate analysis of factors affecting survival using proportional hazards model ($n = 927$)

	No. of deaths	Relative risk	
Age (years)			$\chi^2 = 27·12$, 1 d.f., $P < 0·0001$
≤59	71	1·00	
60–69	150	1·26 (0·95–1·68)	
≥70	351	1·82 (1·40–2·37)	
Stage			$\chi^2 = 242·34$, 4 d.f., $P < 0·0001$
A	23	1·00	
B	114	2·01 (1·27–3·19)	
C	133	3·56 (2·26–5·62)	
'D'	180	11·13 (7·06–17·55)	
Unknown	122	7·15 (4·47–11·43)	
Differentiation			$\chi^2 = 30·60$, 3 d.f., $P < 0·0001$
Well	87	1·00	
Moderate	237	1·09 (0·85–1·40)	
Poor	75	1·89 (1·38–2·58)	
Unknown	173	1·68 (1·28–2·22)	
Mode of admission			$\chi^2 = 46·30$, 1 d.f., $P < 0·0001$
Planned	348	1·00	
Unplanned	224	1·84 (1·54–2·19)	

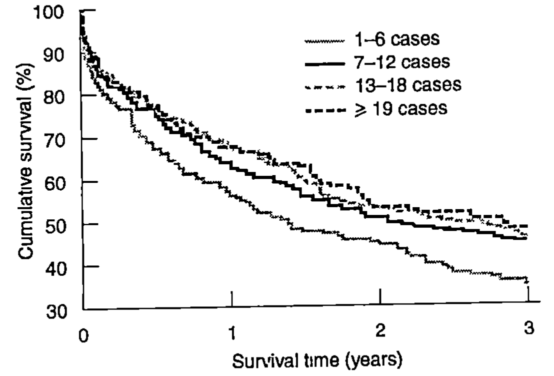
Values in parentheses are 95 per cent confidence intervals

Effect of throughput on outcome

In the univariate analysis, outcome was associated with the number of patients managed by an individual surgeon, although this only just attained significance at the 5 per cent level, but not with hospital throughput (*Figs 1* and *2*). After adjustment for the independent prognostic factors identified in the multivariate analysis, patients managed by consultants with the lowest case load had a worse outcome than those managed by consultants in groups with a greater throughput (*Table 3*), but the relative risk of death was not significantly affected by consultant throughput. Patients managed in hospitals with the lowest throughput had a worse survival than those in hospitals with a greater number of admissions (*Table 3*). However, increasing hospital throughput did not result in a consistent reduction in the relative risk of death.

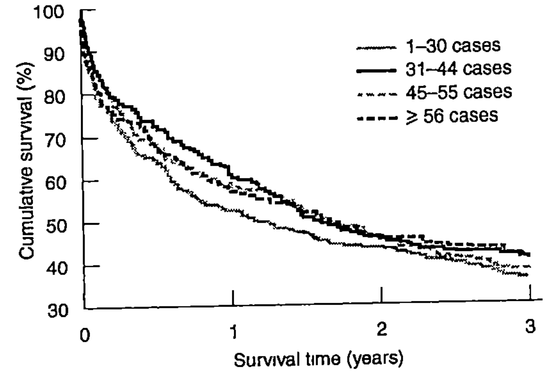
The overall postoperative mortality rate was 12 per cent. Planned admissions had a significantly better postoperative mortality rate than unplanned admissions (9 *versus* 21 per cent; $\chi^2 = 21{\cdot}93$, 1 d.f., $P < 0{\cdot}0001$). There were no significant differences in postoperative mortality rates when the population was stratified by either hospital or consultant throughput, or by mode of admission (*Table 4*).

Table 5 shows the proportion of patients in each throughout group whose management concurred with the three selected process measures. When compared with low-throughput groups, patients managed by surgeons with high workloads or admitted to high-throughput hospitals were significantly less likely to undergo perioperative abdominal ultrasonography or CT and less likely to be operated on 'in hours' by a consultant surgeon following an unplanned admission. The use of APR was not associated with throughput.



No at risk				
1–6 cases	153	86	68	53
7–12 cases	277	175	141	123
13–18 cases	231	155	123	103
≥ 19 cases	151	102	80	73

Fig. 1 Survival by consultant throughput



No at risk				
1–30 cases	231	122	101	82
31–44 cases	236	143	108	95
45–55 cases	247	143	112	93
≥ 56 cases	213	121	98	87

Fig. 2 Survival by hospital throughput

Table 3 Multivariate analysis of relative risk of death during follow-up by consultant surgeon or hospital throughput

	No of consultants	No. of patients	Relative risk*
Consultant (operations)†			
1–6	59	153	1·00
7–12	31	277	0·87 (0·67–1·12)
13–18	15	231	0·87 (0·66–1·13)
≥19	7	151	0·84 (0·62–1·13)
Hospital (admissions)			
1–30	25	231	1·00
31–44	6	236	0·76 (0·60–0·95)
45–55	5	247	0·87 (0·69–1·09)
≥56	3	213	0·80 (0·63–1·02)

Values in parentheses are 95 per cent confidence intervals. *Hazard ratio adjusted for age, mode of admission, stage of disease and tumour grade (degree of differentiation). †Data available for 812 patients operated on; in nine cases the identity of the consultant team was unknown

Table 4 Postoperative deaths by throughput groups

	All cases†	Planned admissions	Unplanned admissions
Consultant (operations)*			
1–6	23 (15)	9 (10)	14 (25)
7–12	29 (11)	15 (7)	14 (22)
13–18	27 (12)	17 (10)	9 (17)
≥19	15 (10)	11 (9)	4 (16)
Hospital (admissions)			
1–30	28 (14)	19 (12)	9 (25)
31–44	20 (9)	10 (7)	9 (17)
45–55	28 (13)	12 (8)	15 (26)
≥56	21 (11)	11 (9)	9 (17)
All cases	97 (12)	52 (9)	42 (21)

Values in parentheses are percentages. †In 26 cases mode of admission was unknown. *Data available for 812 patients operated on, in nine cases the identity of the consultant team was unknown. All significance tests for linear trends $P > 0·05$

Table 5 Proportion of patients managed according to predefined process measures related to throughput groups

	APR*	Scan†	In hours‡
Consultant (operations)§			
1–6	21 (39)	52 (47)	21 (38)
7–12	43 (39)	81 (40)	13 (20)
13–18	34 (33)	53 (32)	15 (29)
≥19	24 (34)	40 (34)	3 (12)
$\chi^2_{\text{linear trend}}$	0·76	6·04	3·78
P	0·38	0·01	0·05
Hospital (admissions)			
1–30	26 (31)	65 (44)	11 (31)
31–44	32 (35)	53 (34)	15 (28)
45–55	30 (34)	69 (43)	20 (35)
≥56	35 (45)	39 (29)	6 (12)
$\chi^2_{\text{linear trend}}$	2·74	5·00	3·46
P	0·10	0·03	0·06
All cases	123 (36)	226 (37)	52 (27)

Values in parentheses are percentages. *Proportion of patients with rectal cancer managed surgically who underwent abdominoperineal resection of the rectum (APR); †proportion of patients with stage A, B or C disease who underwent ultrasonography or computed tomography, ‡proportion of patients with an unplanned admisson whose operation was performed 'in hours' by a consultant surgeon §$n = 812$; in nine cases, the identity of the consultant team was unknown

Discussion

The patient- and disease-related characteristics of this cohort are similar to those reported for another recent population-based series[8]. The present results confirm the importance of known prognostic factors, but do not demonstrate a consistent relationship between survival and the throughput of individual surgeons or that of hospitals.

The use of a cancer registry database allows for the review of the management of a cohort of patients resident in a defined geographical area, and avoids the referral and selection biases which hinder generalization from hospital-derived series. Surveillance databases, however, are subject to misclassification errors and therefore the hospital notes of all patients with cancers recorded as 'gastrointestinal, not otherwise specified' (ICD-9 159) were reviewed.

The analysis of intersurgeon and interinstitutional differences in survival controlled for known confounding factors; these can only be adequately controlled for when they have been accurately defined. In this series possible occult disseminated disease was excluded by abdominal ultrasonography or CT in only 37 per cent of patients with disease recorded as stage A, B or C. Surgeons in the group with the highest throughput were less likely to use imaging modalities to confirm the stage of disease than the baseline group, and so may have understaged a greater proportion of patients under their care. If systematic understaging has occurred, the survival differences between these groups would have been underestimated.

Less frequent use of imaging techniques in hospitals with a high throughput was unexpected. In larger units, competing priorities from other specialties may result in poorer access to diagnostic radiological facilities for patients with colorectal disease. Pressure on radiological services may increase if recommendations for postoperative hepatic surveillance are implemented[7].

The postoperative mortality rate in this series is similar to that in the West Midlands series[9,10] but higher than that reported from Trent and Wales[8]. No association was found between throughput and postoperative mortality rate. These findings concur with those of McCardle and Hole[2] who were unable to relate significant intersurgeon differences in both short-term and long-term outcome to individual surgical volume of work. Hermenek *et al.*[11], Sagar *et al.*[12] and Mella *et al.*[8] were also unable to relate variation in postoperative mortality rates to patient throughput. Hermenek and colleagues[11] reported that patients with rectal cancer operated on by high-throughput surgeons had lower recurrence rates, but this analysis was limited to two-thirds of the original study sample and only partially adjusted for case-mix. The determinants of short-term surgical outcome are more likely to reflect patient physiological status than operator expertise. While it was not possible to collect detailed information on comorbidity in the present study, the distribution of surrogate measures, such as patient age, did not differ substantially across throughput groups (data not shown). Consultants with the lowest throughput, however, were more likely to operate on unplanned admissions because of the need for the non-specialist to provide an on-call service. However, postoperative mortality rate was not associated with throughput irrespective of mode of admission.

This absence of an association between throughput and outcome may reflect the limitations of quantifying surgical expertise in the management of bowel cancer solely in terms of the number of patients with colorectal cancer operated on. Colorectal surgeons also gain surgical expertise through the management of benign colorectal disease. It should be recognized that the number of procedures required to acquire a surgical skill may be very different from that necessary to maintain expertise. Holm *et al.*[13] demonstrated significant differences in outcome in patients with rectal cancer operated on by 'experienced' and 'non-experienced' surgeons which could not be explained by intersurgeon differences in workload.

The apparent lack of association between throughput and outcome in patients with colorectal cancer is in marked contrast to findings in breast[14–16] and testicular[17] cancer. However, the optimal management of breast and testicular disease involves multimodality treatments, and outcome is determined not only by the surgical procedure but also by the appropriate use of adjuvant therapies. The association between throughput and outcome in these circumstances may reflect a greater awareness of the need for a multidisciplinary approach among high-throughput consultants, rather than their greater surgical skill.

In this series only 5 per cent of patients received appropriate postoperative chemotherapy and only 10 per cent of patients with rectal cancer were referred for radiotherapy (data not shown). This is not a criticism, as the evidence base for using these modalities is still being defined. If, as has been suggested, variation in the use of adjuvant therapies could explain up to one-quarter of the intersurgeon differences in survival from breast cancer[14], a relationship between throughput and outcome in colorectal cancer may not be revealed until and unless there is widespread variation in the use of effective adjuvant therapies.

The reorganization of cancer services will, however, make it difficult to disentangle the relative effect on survival of higher throughput and the more widespread adoption of a multidisciplinary approach because surgeons on the cancer team will have a substantially higher patient throughput than 'non-colorectal cancer' colleagues. However, current proposals to change the configuration of cancer services are unlikely to reduce the proportion of emergency admissions. The present findings reaffirm that the poor prognosis for these patients persists even after controlling for patient-, disease- and health service-related factors.

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Editorial Team of the BJS

Original article

Intraoperative lymphatic mapping and the sentinel node concept in colorectal carcinoma

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Background: Orderly progression of nodal metastases has been described for melanoma and breast cancer. The first draining lymph node, the sentinel node, is also the first to contain metastases and accurately predicts nodal status. The aim of this study was to assess the feasibility of lymphatic mapping and sentinel node biopsy in colorectal cancer.

Methods: In 50 patients with colorectal cancer patent blue dye was injected around the tumour. After resection of the tumour the specimen was examined to identify blue-stained lymph nodes. Routine histopathological examination was performed on all nodes and the blue, haematoxylin and eosin-stained tumour-negative nodes were tested immunohistochemically.

Results: Lymphatic mapping was possible in 35 of 50 patients (70 per cent). Pathological examination with haematoxylin and eosin staining showed lymph node metastases in 20 of 35 patients. In eight of these 20 patients the blue nodes showed tumour, while in 12 the blue nodes were not involved. This represents a false-negative rate of 60 per cent.

Conclusion: Lymphatic mapping using patent blue dye is feasible in colorectal cancer. The blue-stained nodes do not predict nodal status of the remaining lymph nodes in the resected specimen. The concept of lymphatic mapping and sentinel node identification is not valid for colorectal cancer.

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Introduction

In colorectal cancer the presence of lymph node metastases has a major impact on prognosis[1]. Moreover, nodal status determines the need for adjuvant therapy after surgical resection of the tumour. Considering the developments in adjuvant treatment, it is crucial to get accurate information regarding lymph node status in patients with colorectal cancer[2].

Curative resection for colorectal cancer should include removal of the lymphatic drainage of the tumour-bearing segment of bowel. The exact extent of the lymphadenectomy required for colorectal cancer, however, remains a matter of debate[1,3,4]. As regards histopathological examination of the resected specimen, there are no exclusive criteria for the minimum number of lymph nodes to be examined per specimen[5,6]. Since the chance of finding tumour-positive nodes rises as the total number of lymph nodes examined increases, it is advisable to harvest as many lymph nodes as possible from the specimen[5–7].

One way of retrieving a large number of lymph nodes is to use the clearing method. In this procedure the fat tissue is dissolved, using acetone and alcoholic solutions, so vessels and lymph nodes can be detected easily[5–9]. An equivalent number of lymph nodes can be obtained by very careful manual dissection[10]. These methods, however, are time consuming and currently not in general use.

Morton *et al.*[11] introduced the sentinel node biopsy for staging patients with melanoma. The concept of this technique is based upon the orderly progression of tumour cells within the lymphatic system. The first draining node, called the sentinel node, is also the first to contain metastases. Identifying the sentinel node can be accomplished by preoperative injection of ^{99m}Tc-radiolabelled colloidal albumin at the site of the primary melanoma and subsequent intraoperative use of a handheld γ probe to localize radioactivity in the lymph node region. The technique can also be performed with a vital blue dye, which enables visualization of the lymphatics[12].

Sentinel node biopsy is also performed in patients with breast cancer, as well as in those with penile and vulvar cancer[13–15]. The histological status of the sentinel node accurately predicts the lymph node status. Moreover, in breast cancer additional immunohistochemical analysis of the sentinel node identified significantly more patients with lymph node metastases than routine histopathological processing of the lymph nodes[16].

The purpose of this study was to determine whether the concept of intraoperative lymphatic mapping in patients with primary tumours of the colon and rectum is feasible. Moreover, the predictive and complementary value of the designated sentinel node was investigated to evaluate whether examination of the sentinel node could simplify and/or improve pathological staging in colorectal cancer.

Patients and methods

From June 1997 to November 1997, 50 consecutive patients presenting with colorectal cancer were enrolled into the study. Informed consent was obtained from all patients.

Patients with primary adenocarcinoma of the colon or rectum were studied. Patients with more than one primary tumour and those in whom only a small part of the mesocolic or mesorectal tissue was resected were excluded. Lymphatic mapping was performed with patent blue dye (Bleu patenté V; Laboratoire Guerbet, Aulney-Sous-Bois, France). In colon cancer the dye was injected subserosally at four sites close to the tumour, shortly after exposing the tumour-containing bowel segment. In the case of distal rectal cancers the dye was injected before operation into the submucosa just beneath the tumour edge under proctoscopic view. The total amount of patent blue dye injected varied from 1 to 2 ml.

After injection of the dye, the surgeon proceeded with the resection of the tumour-containing bowel segment, looking for blue-stained nodes and lymph vessels in the mesocolic tissue. The minimum time from injecting the dye until transection of the vascular trunk was 15 min.

After resection of the tumour the specimen was examined by the pathologist and one of the authors (J.J.A.J.). The specimen from the first ten patients was put in an acetone solution for 24 h to clear the fat of mesocolic tissue in order to increase the yield of lymph nodes. However, because the acetone was found to partially dissolve the blue dye all other specimens were dissected immediately following resection. Blue nodes were traced within the entire mesocolon or mesorectum, following the point of vessel ligation down to the bowel wall. All lymph nodes, including blue ones, were embedded separately for preparation of paraffin sections and staining with haematoxylin and eosin.

Additional immunohistochemical staining for cytokeratins was performed on single-level sections from blue-stained nodes of 27 haematoxylin and eosin-stained tumour-negative specimens. Antibodies against cytokeratin p (Lü-5) and cytokeratin 19 (RCK 108) (both produced by Biogenex, San Ramon, California, USA) were used. A second haematoxylin and eosin-stained section from the same level of the lymph node was examined to determine whether or not the detection of metastases in immunohistochemical stains was due to the examination of different tissue levels only or to the greater sensitivity of the staining method used.

Results

In 35 (70 per cent) of 50 patients blue-stained nodes were identified at dissection of the specimen. In patients with rectal cancer patent blue injection proved difficult owing to the location of the tumour, resulting in a higher failure rate. Tumour stage and differentiation did not seem to influence the feasibility of lymphatic mapping (*Table 1*). In nine of the 15 unsuccessful procedures the dye was injected directly into the bowel lumen instead of subserosally, as seen during macroscopic examination.

In cases in which the lymphatic mapping procedure was successful the number of blue-stained lymph nodes ranged from one to 16 (median three blue nodes per specimen). The total number of lymph nodes removed per specimen varied from two to 37, with a median node count of 14

Table 1 Tumour characteristics and number of successful lymphatic mappings

	No. of patients (*n* = 50)	No of successful mappings (*n* = 35)
Tumour site		
Right colon	19	13 (68)
Transverse colon	3	2 (67)
Left colon	22	17 (77)
Rectum	6	3 (50)
Tumour differentiation		
Well	4	2 (50)
Moderate	36	26 (72)
Poor	10	7 (70)
TNM stage*		
I	10	7 (70)
II	13	8 (62)
III	21	16 (76)
IV†	6	4 (67)

*Histopathological staging for lymph node metastases according to standard haematoxylin and eosin staining. † In this group one patient had distant metastases without lymph node metastases so the total number of patients with lymph node metastases is 26. TNM, tumour node metastasis (mean node count 13 in manually dissected specimens and 20 in fat-cleared specimens). Blue nodes were mainly located within 3 cm of the tumour margin. However, occasionally they were also located at the mesenteric root.

Twenty-six patients had nodal metastases, five of whom had concurrent liver metastases. One patient had liver metastases without detectable lymph node involvement. Most of the tumour-positive nodes were found close to the tumour. However, in some cases the nodes in the vicinity of the primary were free from tumour, while involved lymph nodes were detected more proximally along the vessels or more laterally in the pericolic fat.

In 20 of the 26 patients with lymph node metastases (haematoxylin and eosin stained) lymphatic mapping had been successful and blue-stained nodes were identified. In only eight of the 20 specimens did the blue-stained nodes contain tumour. In the remaining 12 patients the blue-stained nodes were tumour negative by haematoxylin and eosin staining (*Table 2*).

To assess whether immunohistochemical staining of the presumed sentinel nodes could improve tumour staging in patients with node-negative status according to haematoxylin and eosin staining, the specimens from these patients were also stained for cytokeratins. The results of the entire group of 35 patients in whom lymphatic mapping was successful are given in *Table 3*. Of 15 patients with tumour-negative lymph nodes identified by haematoxylin and eosin staining, immunohistochemical staining of the blue nodes identified two patients with micrometastatic disease. Hence tumour stage had to be altered in two of 15 patients who were originally described as lymph node negative.

Table 2 Results of sentinel node examinations in patients with lymph node metastases and successful lymphatic mapping (n = 20)

		Patients with blue nodes	
Primary tumour*	Patients with tumour-positive nodes (H & E) (n = 20)	Tumour-positive nodes (H & E) (n = 8)	Tumour-positive nodes (H & E or immuno†) (n = 10)
T_1	0	0	0
T_2	0	0	1
T_3	16	4	5
T_4	4	4	4

*According to the American Joint Committee on Cancer/Union Internacional Contra la Cancrum tumour node metastasis classification. †Immunohistochemical staining using antibodies against cytokeratins p (Lu-5) and 19 (RCK 108). H & E, haematoxylin and eosin

Discussion

The sentinel node procedure has proved to be a reliable method of detecting clinically occult lymph node metastases in patients with melanoma[11]. Sentinel node mapping also appears to predict lymph node status in breast cancer and cancer of the penis and vulva. The clinical relevance of the sentinel node lies in the extent of the lymphadenectomy and in decision making for the administration of adjuvant treatment[13–15].

The purpose of sentinel node identification in colorectal cancer would be to improve staging rather than to minimize the extent of lymphadenectomy. Hence, the aim of this study was to investigate whether the detection of a sentinel node could provide more accurate staging by focusing on specific lymph nodes in the resection specimen which are most to likely contain tumour metastases.

The study demonstrates that lymphatic mapping in colorectal cancer is feasible. The success rate of staining lymph nodes approaches 70 per cent with the use of patent blue dye only. In early studies in melanoma and breast cancer success rates of 82 and 66 per cent respectively were achieved[11,13]. With regard to the injection technique, there seems to be a learning curve. Surgeons performing more lymphatic mappings had a higher success rate in staining blue nodes than colleagues who only occasionally injected the blue dye. Most of the unsuccessful mappings resulted from an incorrect injection technique. When injected properly into the bowel wall, only 10 per cent of the specimens did not show any stained lymph nodes.

Table 3 Histopathological analysis of lymph nodes in patients with successful lymphatic mapping (n = 35)

	Non-blue nodes		
	Tumour negative (H & E)	Tumour positive (H & E)	Total
Blue nodes			
Tumour negative (H & E)	15	12	27
Tumour positive (H & E)	0	8	8
Tumour negative (immuno*)	13	12	25
Tumour positive (immuno*)	2	8	10

*Immunohistochemical staining using antibodies against cytokeratins p (Lu-5) and 19 (RCK 108). H & E, haematoxylin and eosin

Of all patients in whom lymphatic mapping was successful, 20 patients showed lymph node metastases (haematoxylin and eosin staining). However, in only eight of these 20 patients were metastases also identified in the blue-stained nodes, giving a false-negative rate of 60 per cent. This figure, combined with the meagre 55 per cent positive predictive value, establishes that the blue nodes identified in colorectal cancer do not predict the nodal status of the patient. These blue nodes cannot be termed true sentinel nodes. These results are in sharp contrast with the low false-negative rates described in other sentinel node studies, with values ranging from 0 to 4 per cent[11–13,17].

Several observations could explain this high rate of tumour-negative blue nodes in node-positive patients. In seven of 12 patients with false-negative blue-stained nodes, extranodal growth and/or gross tumour invasion of the non-blue nodes was noticed. When obvious nodal metastases are present, the lymph flow through these nodes may be obstructed and the lymph will drain through alternative pathways[18]. For these reasons sentinel node biopsy is generally not performed in patients with breast cancer with clinically suspect lymph nodes[17,19]. However, in colorectal cancer it is impossible to select this group of patients before or even during operation. Palpation of the mesocolon or mesorectum does not usually give a reliable impression of nodal status in these patients[20].

Another possible explanation for the lack of a sentinel node may be that the site of injection and subsequent pattern of drainage of the blue dye does not exactly match the lymphatic drainage from the tumour. It seems almost impossible to get round this difficulty, since injection of the blue dye directly into the tumour mass does not result in staining of any lymph nodes. Moreover the route of lymph flow could possibly alter with growth of the tumour into the bowel wall. It is conceivable that several alternative lymphatics are involved in draining the tumour and that these routes alter during tumour progression, especially for large growths.

Additional immunohistochemical staining of the identified blue nodes did reveal two patients with micrometastases that were negative with routine haematoxylin and eosin staining. In melanoma and breast cancer more detailed staging has been described using immunohistochemical analysis[11,16,21,22]. In colorectal cancer the prognostic value of additional immunohistochemistry is still uncertain[23–26].

It is concluded that with the above described technique, identification of the sentinel node in colorectal cancer is unreliable. The sentinel node concept seems only applicable in a limited subset of (skin-derived) cancers and caution must be taken in extrapolating this technique to other types of malignancy.

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Lateral ligaments of the rectum: an anatomical study

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Background: The lateral ligaments of the rectum are surrounded by confusion and misconception. Their identification before 'hooking them on the finger', clamping and ligating is considered in many surgical texts to be an essential step in mobilization of the rectum. By contrast, it is the experience of many colorectal surgeons that the mesorectum can be dissected out either by diathermy or sharp dissection alone.

Methods: Dissection in the mesorectal plane was performed on 28 cadaveric pelves.

Results: In ten of the pelves, no connective tissue structure crossed from the pelvic side wall to the rectum. The remaining 18 had only very insubstantial connective tissue strands crossing this space. A total of 17 middle rectal arteries were found, all of them unilateral. Fourteen of these vessels crossed the mesorectum independent of any structure, while the remainder were part of a neurovascular bundle with a connective tissue element.

Conclusion: It is proposed that the 'lateral ligaments' of the rectum do not exist and that the term should be dropped from surgical texts. When present, the middle rectal artery is a small vessel, close to the pelvic floor. The entire rectum may be mobilized by sharp dissection without the need for clamping or ligation of any significant structure.

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Introduction

Local recurrence of rectal cancer represents a failure of surgery. McFarlane *et al.*[1] have undertaken a prospective study of total mesorectal excision and reported results for the period 1978–1991 of 290 consecutive cancer referrals. Among the 211 patients who had undergone potentially curative surgery (i.e. the surgeon believed that at the end of the procedure all grossly visible cancer had been removed) the local recurrence rate was 4 per cent[1]. These results were attributed to a total excision of the visceral mesentery of the rectum – the mesorectum. This fatty lymphovascular tissue is the probable source of the much higher rates of pelvic recurrence seen in other studies, even when this less radical surgery is combined with adjuvant therapy[2].

Heald and colleagues[3] advocate that the mesorectum is best dissected under direct vision with sharp scissors and that digital blunt dissection should be avoided as this could tear veins or split into tumour planes. Most modern texts contradict this view and state that in the final step of mobilization of the rectum 'the lateral ligament on each side of the rectum is hooked on the finger, clamped and divided'[4].

Little is known of the morphology of the lateral ligaments and controversy exists regarding their relationship to the middle rectal artery. The aim of this study therefore was to define the anatomy of the lateral ligaments and the middle rectal arteries, and ascertain any relationship between the two.

Materials and methods

Twenty-eight cadavers embalmed in formalin were studied, 11 male and 17 female. The median age at death was 86 (range 64–100) years. All were Caucasian. Each pelvis had been sectioned in the sagittal plane, and both hemipelves were examined.

The peritoneum was divided at the pelvic brim and the mesorectum dissected down to the pelvic floor. Loose areolar tissue was divided, but any other structures crossing the mesorectal space were preserved for subsequent study. In each case, the lateral ligaments, the autonomic nerves and the middle rectal arteries were sought. The superior and inferior rectal arteries were also identified.

The morphology and distance of these structures at the rectal side wall above the pelvic floor was measured. Their direction of travel was also recorded.

Results

No structures in any of the 28 pelves corresponded to the textbook descriptions of the lateral ligaments.

Only insubstantial connective tissue strands were found traversing the space between the mesorectum and the pelvic side wall in a proportion of specimens. Even these structures were found to be absent bilaterally in ten pelves. They were found unilaterally in 15 pelves and bilaterally in a further three. There were a total of 30 bands in these 18 specimens, with between one and five bands in each. The median height of these bands above the anorectal junction was 4 (range 0–10) cm. Seventeen of these bands were lateral to the rectum, ten posterior and three posterolateral.

Middle rectal arteries were found in 17 of the specimens, in every case as a unilateral structure. Nine were found in female and eight in male pelves. Fourteen of these middle rectal arteries crossed the mesorectal plane independent of any connective tissue structure. The remaining three were part of a neurovascular bundle with a connective tissue element. The median height of these vessels above the pelvic floor was 2 (range 0–7) cm. Their median diameter was 1 (range 0·5–2) mm. Twelve of these middle rectal arteries approached the rectum from a lateral direction, three anterolaterally and two from posterolaterally.

The branching pelvic splanchnic nerves were visualized in each pelvis. They arose posterior to the origin of the middle rectal vessels, and were observed to run in an anteromedial direction. They reached the rectum itself at a similar height above the pelvic floor as the middle rectal vessels. In the three cases described above, these nerves contributed towards a neurovascular bundle with a connective tissue element. In every other case, these nerves traversed the areolar tissue of the mesorectum independently of any connective tissue or vasculature.

Discussion

Little original work exists on the anatomy of the lateral ligaments. *Gray's Anatomy*[5] states that 'around the middle rectal vessels, fascia extends from the posterolateral pelvic wall (level with the third sacral vertebra) to the rectum as the lateral rectal ligaments'. From a surgical standpoint, Goligher and Duthie[6] describe these structures, as seen from above after 'a certain amount of definition', as having 'a roughly triangular shape with the base on the pelvic side wall and the apex joining the side of the rectum'. By contrast, in the present study no significant structures crossing the mesorectal plane were identified. Insubstantial thin strands of connective tissue were sometimes found, but could not be thought to represent the lateral ligaments for a number of reasons. Most importantly, these strands of connective tissue were no different from those one would expect to find in any areolar plane. Furthermore, their extreme variability both in terms of their height above the pelvic floor and direction of travel suggested that they were not constant structures. Indeed, they were often absent altogether.

There is significant variation in published data on the incidence of the middle rectal artery. The range is from 12 per cent[7] to 100 per cent[8] of pelves. This probably reflects variation in the concept of what constitutes a vessel and differences in the method used to trace them. The present finding of a unilateral middle rectal artery in a little over half of the pelves is supported by the work of DiDio *et al.*[9] (57 per cent) and Vogel and Klosterhalfen[10] (50 per cent). It is interesting to note that this vessel, when present, never exceeds 2 mm in diameter. In some respects the present findings are similar to those of Boxall *et al.*[11] who conducted a very detailed study of the middle rectal artery. The middle rectal artery is generally small, and at or just above the pelvic floor. However, the authors found no evidence of any 'accessory middle rectal artery' nor were any structures found that could be termed a lateral ligament.

The relationship of the middle rectal artery to the lateral ligaments is also the subject of some controversy. The majority view is that the middle rectal vessels run in the lateral ligaments[5]. Boxall and colleagues[11] take a different view, claiming the lateral ligaments contain only accessory branches of the middle rectal artery, found in about 25 per cent of pelves. They describe the middle rectal vessels as crossing the mesorectum in condensations of fascia, although quite separately from the lateral ligaments. In this study, the middle rectal artery crossed the mesorectal plane independently of any connective tissue structure.

Tiny branches from the autonomic pelvic plexi were seen crossing to the rectum. These structures were almost universally found to be distinct from the middle rectal vessels throughout their length and to have no association with connective tissue. They therefore cannot be confused with any 'ligamentous' structure and certainly do not require ligation and clamping as described in surgical texts. The authors do not believe therefore that they in themselves represent a lateral ligament[12] or could be considered a structure a surgeon could 'hook' a finger around. These results are in accord with the postulate that the lateral ligament is nothing more than a surgical artefact that results from injudicious dissection.

Taken together, these findings suggest that the lateral ligaments of the rectum do not exist. There is no anatomical argument against sharp dissection in the mesorectal plane and as a rule there is no vessel that requires clamping. By 'hooking' the finger into the tissue lateral to the rectum it may be that the surgeon encounters mesorectal vessels and creates an artefactual ligament. This obviously raises the grave concern that such blunt dissection results in mesorectal tissue being left behind and increases the risk of local recurrence and severe autonomic nerve injury.

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Original article

Anocutaneous advancement flap closure of high anal fistulas

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Background: Fistula-*in-ano* may be treated by closing the internal fistulous opening. An anocutaneous flap was developed to facilitate this closure.

Methods: From October 1995 to April 1997, 40 patients with high trans-sphincteric or suprasphincteric anal fistulas were treated. The important components of the procedure are excision of the internal opening, excision or curettage of the tract, closure of the internal opening by an anocutaneous flap, and external drainage.

Results: In two patients (5 per cent) the flap separated and the sutured internal opening was exposed. One of the two was healed 4 weeks later. In the remaining 38 patients, complete healing occurred 2–3 weeks after operation. No patient was incontinent of gas or stool.

Conclusion: This procedure is technically simple, heals rapidly with minimal scarring, and cures anal fistulas while preserving the anal sphincter.

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Introduction

Most anal fistulas can be managed by 'laying open' the tract. But in high trans-sphincteric or suprasphincteric fistulas, laying open involves division of most of the anal sphincter muscles and may result in incontinence. In these circumstances it may be necessary to consider sphincter-preserving techniques. A simple technique, which uses an anocutaneous flap for anal fistulas, has been developed.

Patients and methods

Patients

From October 1995 to April 1997, 40 patients with anal fistula were treated with the following procedure. There were 38 men and two women with a mean age of 39 (range 22–71) years. No patient had inflammatory bowel disease. Ten patients had a history of previous operations for fistula. The tracts were high trans-sphincteric in 35 and suprasphincteric in five.

Operative technique *(Fig. 1)*

Preoperative preparation consists of a full mechanical bowel lavage and intravenous antibiotics. The patient is placed in the prone jack-knife position under epidural anaesthesia. The tract is identified, and the internal opening in the anal canal is exposed using a bivalved anal retractor.

An inverted U-shaped incision is made in the anoderm and the perianal skin with an apex 2–2·5 cm in width. An anocutaneous flap including part of the thickness of the internal sphincter and the perianal fat is then raised. The main tract is excised or curetted, and the internal opening in the flap is excised. The muscular defect at the previous internal opening is sutured with interrupted 4/0 polyglactin sutures. The mobilized flap is then advanced over the closed internal opening and approximated to the anal mucosa and underlying internal sphincter with interrupted 3/0 polyglactin sutures. Further advancement is gained by excising Burow's triangles of skin from the adjacent base. This is required in approximately two-thirds of cases (24 of 40). The sides of the flap are also sutured sparsely. A Penrose drain is placed in the external opening.

After operation the patient is maintained on intravenous therapy and no oral nutrient is permitted for 3 days to ensure adequate healing of the flap. As soon as the patient has passed stool (usually 5 days after operation) sitz baths or showers are prescribed, and the patient is discharged from hospital. The first digital and/or anoscopic examination is done 10–14 days after operation to check suture lines.

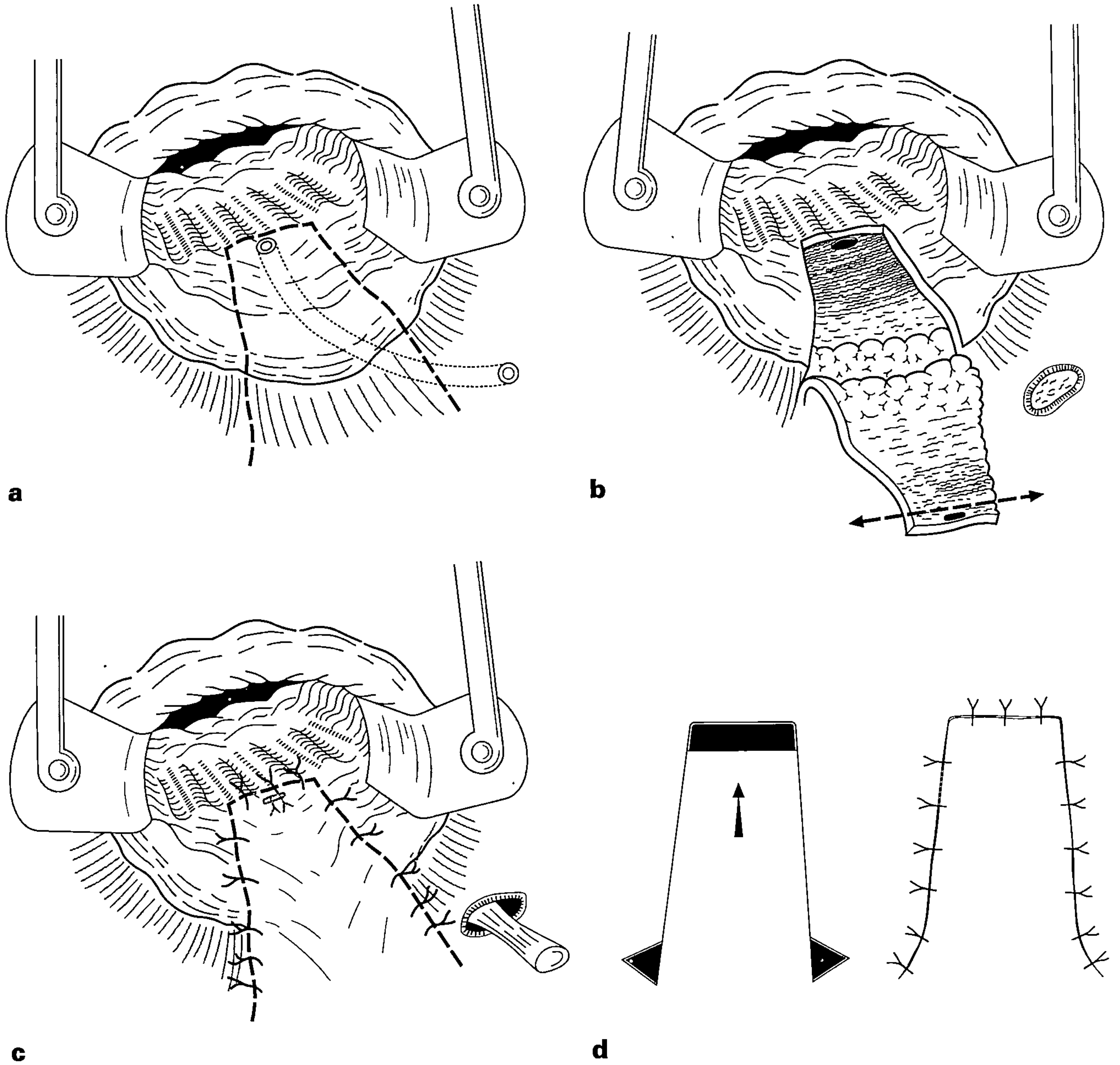

Fig. 1 Anocutaneous advancement flap. **a** The dotted line outlines the flap to be raised. An internal opening is at the dentate line. **b** An inverted U-shaped flap is elevated. The tract is excised or curetted. The internal opening in the flap is excised. **c** The defect in the internal anal sphincter is sutured. The flap is drawn up into the anal canal and approximated to the anal mucosa and underlying internal sphincter proximal to the muscle sutures. **d** Further advancement is gained by excising Burow's triangles of skin from the adjacent base

Results

The mean length of follow-up was 17 (range 6–24) months. In two patients (5 per cent) the flap separated and the sutured internal opening was exposed on anoscopic examination. One was a 71-year-old man with a transsphincteric fistula with horseshoe extension. Digital and anoscopic examination were done weekly. The internal opening was closed with epithelization 4 weeks later. The other was a 43-year-old man with a trans-sphincteric fistula with left ischiorectal extension. He had a history of previous fistula operation, and had a large high-lying internal opening. The internal opening was not closed and a 2-cm sinus remained.

In the remaining 38 patients, complete healing occurred 2–3 weeks after operation. Although the suture line of the apex had occasionally fallen apart, the internal opening was well covered by the flap. No patient was incontinent of gas or stool.

Discussion

Most anal fistulas arise as a result of chronic infection of an intersphincteric anal gland[1]. But persistence may be related more to non-specific epithelization of the tract than to a chronically infected anal gland[2]. The fistulas are cured by closing the internal opening after eradication of cryptoglandular infection.

The internal opening can be closed by simple sutures[3] or by a more secure method using various mucosal[4–6] or skin[7] flaps. The results of mucosal advancement flap in non-inflammatory bowel disease are excellent, but the procedure is often difficult to perform and has a risk of ectropion. With an island flap, a large perineal wound would be left.

This procedure is technically simple. It is necessary to follow the basic principles of flap surgery, including attention to length : width ratio, thickness, tension, etc. The flap includes part of the internal sphincter and the perianal fat. Excising a partial thickness of the internal sphincter does not adversely affect continence, but might add to the viability of the flap. The tension of the flap took advantage of skin elasticity. In two-thirds, further advancement was gained by excising Burow's triangles of skin from the adjacent base[8].

The major cause of flap failure is inadequate blood supply, an intrinsic factor. In clinical practice, clinical judgement such as observation of colour, capillary blanching and refill, warmth, and bleeding from a stab wound is most important for flap circulation[9]. In the present patients the suture line of the apex occasionally fell apart, but the internal opening was well covered by the flap, and healed. In only two patients did the flap separate and expose the sutured internal opening. The internal opening was closed with epithelization in one of the two patients. The authors consider that the flap may have protected the internal opening while it closed.

No patient complained of minor symptoms of anal incontinence because no sphincter division was required. The primary closure offered rapid wound healing and no residual scarring.

This procedure is most suitable for high trans-sphincteric or suprasphincteric anal fistulas in which internal openings are at the dentate line. It also seems appropriate for anterior fistulas in women. On the other hand, fistulas with an internal opening that is large or high in the anal canal can sometimes be difficult to treat with this procedure. When there is severe perianal scarring at the flap site due to previous fistula surgery, the flap cannot be raised safely. Although there were no fistulas with inflammatory bowel disease in the present patients, these fistulas could be treated successfully by this procedure in selected patients.

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Original article

Fertility after ileal pouch–anal anastomosis in women with ulcerative colitis

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Background: Women with ulcerative colitis are believed to have normal fertility but colectomy and ileal pouch–anal anastomosis (IPAA) may impair fertility. The aim was to compare fertility in patients with ulcerative colitis before and after IPAA with that in the national population.

Methods: Some 258 consecutive women who had undergone IPAA for ulcerative colitis were identified. Data were collected by questionnaire and from medical records. The observed number of births was compared with the number expected by indirect standardization by age and calendar year. Fertility from the age of 15 years to colectomy, from the onset of ulcerative colitis to colectomy, and from the 12 months after stoma closure to the time of data collection was investigated.

Results: A total of 237 women (92 per cent) responded. From the age of 15 years to colectomy there were 251 deliveries compared with an expected number of 286 ($P < 0{\cdot}05$). The number of births from the onset of ulcerative colitis to colectomy was 120, compared with an expected 131 ($P > 0{\cdot}3$). From the 12 months after ileostomy closure until data collection there were 34 deliveries, compared with an expected 69 ($P < 0{\cdot}001$).

Conclusion: There is a considerable reduction in postoperative fertility after restorative surgery for ulcerative colitis.

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Introduction

Previous fertility studies on women suffering from inflammatory bowel disease suggest that fertility is unaffected by ulcerative colitis[1–4]. Ileal pouch–anal anastomosis (IPAA) is frequently used following proctocolectomy, and pregnancy and childbirth are safe after IPAA[5–10]. Reports exist, however, which suggest that fertility could be impaired after both IPAA[11,12] and conventional proctocolectomy[13], but consistent data on fertility after IPAA are not available.

The aim of this study was to evaluate preoperative and postoperative fertility in women with ulcerative colitis who underwent IPAA by comparing the actual number of births with the birth rate in the general female population.

Patients and methods

The study involved women from two surgical units in Aarhus, Denmark (86 patients) and Göteborg, Sweden (172 patients). All women with ulcerative colitis who had restorative surgery with proctocolectomy and IPAA between November 1982 and June 1996 were included. Data concerning births, possible postoperative *in vitro* fertilization (IVF) and onset of ulcerative colitis were obtained by means of questionnaires. The following time ranges were determined from medical records: (a) from the age of 15 years to colectomy ('preoperative') (mean 17·2 (range 0–35) years); (b) from the onset of ulcerative colitis to colectomy (i.e. 'during ulcerative colitis') (mean 7·8 (0–31·4) years); and (c) from the 12 months after stoma closure until data collection or age 50 years ('corrected postoperative') (mean 4·6 (range 0–12) years). Fertility rates were compared with external references (national data)[14,15]. The observed number of births in the study group was compared with the expected rate. The expected number of births was calculated by summing the products of the age, country and calendar-year population birth rates and the corresponding study group age-specific person-years of exposure (indirect standardization by age, country and calendar year).

Data were compared with the χ^2 test; $P < 0{\cdot}05$ was considered statistically significant.

Results

Of the 258 patients asked to participate, 237 (92 per cent) responded. There was an equal response rate at the two hospitals.

Fertility data are shown in *Table 1*. The preoperative reduction in the number of births to 87 per cent of that expected was significant ($P < 0{\cdot}05$). During ulcerative colitis there was no significant reduction in the number of births. For the corrected postoperative period, the birth rate was reduced to 49 per cent of that expected, a highly significant reduction ($P < 0{\cdot}001$). When children born following IVF were excluded, the observed number of births in the corrected postoperative period was reduced to 35 per cent of that expected ($P < 0{\cdot}001$). After operation 29 per cent of the children were born following IVF.

There were slight differences between the two populations before operation. In Aarhus the observed numbers of births before operation and during ulcerative colitis equalled that expected, while in Göteborg the rate was approximately 15 per cent below that expected. However, the birth rate excluding IVF in the corrected postoperative period was the same at the two hospitals.

The mean time from onset of ulcerative colitis to colectomy was 5·2 years in Aarhus and 9·2 years in Göteborg. Mean age at operation was 30·8 and 34·7 years in Aarhus and Göteborg respectively.

Discussion

The main finding in the present study was a markedly reduced postoperative fertility rate in women who underwent IPAA for ulcerative colitis. Patients from two surgical units were studied, and the response rates as well as the observed : expected ratio of births (excluding births following IVF) for the corrected postoperative periods were the same for the two units. This is important for the interpretation of the results, and further strengthens the validity of the findings.

Twenty-nine per cent of births in the corrected postoperative period occurred after IVF, whereas only about 1 per cent of all births in Denmark and Sweden occurred after IVF for the years involved in this study. The high rate of IVF in patients with IPAA strongly indicates that these patients have a wish for children as well as significant fertility problems.

Although preoperative fertility was significantly reduced ($P < 0{\cdot}05$), the actual number of births was only moderately reduced, to 87 per cent of the number expected. Furthermore, the reduction during ulcerative colitis was not significant, in concordance with previous findings[1–4]. However, the slight but statistically significant reduction in the overall preoperative period remains unexplained.

Reports on female fertility after IPAA are scarce and inconclusive[7,11,12]. However, the large North American studies on IPAA include several hundred women operated on, whereas the reported number of postoperative births is seemingly low. Counihan *et al.*[12] reported 23 postoperative deliveries by 19 of 206 women; Scott *et al.*[6] reported 16 postoperative deliveries by 12 of 330 women; and Juhasz *et al.*[5] reported 53 postoperative deliveries by 43 of 577 women. Thus the reported number of deliveries in these studies appears to be similar to that in the present study, with 34 postoperative deliveries in 237 women.

In view of the normal fertility rate for patients with ulcerative colitis reported by other studies[1–4] and the moderate (but statistically significant) preoperative reduction in fertility found in the present study, it seems

Table 1 Expected and observed numbers of births for the different observation periods

Observation period	Expected	Observed	Observed/expected ratio	*P*†
Preoperative	288	251	0·87 (0·77–0·99)	< 0·05
During ulcerative colitis	131	120*	0·91 (0·77–1·10)	> 0·30
Corrected postoperative	69	34	0·49 (0·35–0·69)	< 0·001
Corrected postoperative excluding IVF	68	24	0·35 (0·24–0·53)	< 0·001

Values in parentheses are 95 per cent confidence intervals. *Includes four births in patients with onset of ulcerative colitis during pregnancy. IVF, *in vitro* fertilization. †χ^2 test reasonable to relate the severely reduced postoperative fertility to the surgical procedures.

In a study of 21 women who had IPAA for ulcerative colitis, postoperative hysterosalpingography gave normal findings in only seven[11]. If this finding is applicable to larger groups of patients, it suggests that postoperative fertility could be severely reduced as a result of occlusion of the fallopian tubes.

The impact of the surgical procedures on the sexual life of the patients is not clear. There have been reports of a better sexual life after operation compared with the time during ulcerative colitis[7,16], but dyspareunia might be more frequent after operation[12]. However, it does not seem likely that a decrease in sexual activity can explain the reduced fertility rate found in the present study.

Other possible explanations for the severely reduced postoperative fertility could be that the patients hesitate to become pregnant because they are frightened to pass on ulcerative colitis to their children. They might have been advised against pregnancy by doctors who were unaware that pregnancy after IPAA is safe[5–10,12]. In view of the high frequency of postoperative IVF, it is unlikely that the majority of these women do not wish to have children.

The authors suggest that anatomical changes due to adhesions is the main explanation for the present findings; but further studies are required to clarify the causes (physical, sociodemographic, or both) for the reduced numbers of children born after IPAA.

In conclusion, the postoperative fertility rate was markedly reduced following IPAA for ulcerative colitis. The data indicate that the risk of reduced fertility and possible treatment should be included in the information given to women with ulcerative colitis before operation.

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Original article

Topographical distribution of blood supply to the anal canal

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Background: It has been suggested that anal fissure is an ischaemic ulcer caused by a combination of poor blood supply to the posterior midline of the anal canal and spasm of the internal anal sphincter. This study investigated the topographical distribution of blood supply to quadrants of the anal canal above and below the dentate line.

Methods: Cadaveric anal canals were removed and 1-cm blocks were cut above and below the dentate line. Blocks were sectioned at 10 μm and every 25th section was mounted. Using the technique of systematic random sampling, fields in the subanodermal space and the internal anal sphincter in posterior, lateral and anterior quadrants of the anal canal were chosen. The numbers of small arterioles in each field were counted. Mean counts were compared for both subanodermal space and internal anal sphincter between quadrants and levels above and below the dentate line using Page's *L* test for trends.

Results: Anal canals from eight cadavers were examined. There was a significant trend to an increasing number of arterioles from posterior to anterior in the subanodermal space at all levels and at two of three levels in the internal anal sphincter.

Conclusion: The arteriolar density is less in the posterior quadrant throughout the anal canal. It may be that this poor blood supply predisposes to the development of anal fissures at their most common site in the posterior midline.

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Introduction

Anal fissure is a split in the skin of the distal anal canal characterized by pain on defaecation and rectal bleeding. Recently it has been hypothesized that anal fissure may be an ischaemic ulcer caused by the combination of spasm of the internal anal sphincter (IAS) and poor blood supply to the posterior midline of the anal canal, the site at which the majority of fissures occur[1,2]. Only one study has previously examined the topography of the inferior rectal artery using post-mortem angiography[1]. Two distinct distributions of the blood supply to the anal canal were reported. In 15 per cent both the anterior and posterior midline of the anal canal were well supplied by branches of the inferior rectal artery. However, in the remainder (85 per cent) the posterior midline was poorly supplied. As anal fissure is a mucosal ulcer, the blood supply in the subanodermal space may also be deficient relative to that in other quadrants of the anal canal. This study aimed to examine arteriolar density in the posterior, lateral and anterior quadrants of the subanodermal space and IAS above and below the dentate line.

Materials and methods

Preparation of specimens

The rectum and anal canal were removed *en bloc* from embalmed cadavers. The specimens were opened along the anterior midline and the dentate line was identified. Specimens were then transected at 1-cm intervals above and below the dentate line for the length of the anal canal. Blocks were fixed in specipolymer wax and sliced on a microtome at 10 μm thickness. Every 25th section was mounted on a glass slide and stained with haemotoxylin and eosin.

Arteriole counting and minimization of bias

The technique of systematic random sampling was used to minimize bias[3]. One of every four slides was to be examined to ensure that arterioles in greater than ten sections per block were counted. Numbers from 1 to 4 were placed on paper and drawn from a 'hat'. Every fourth slide from the initial starting point was then examined. Arterioles were identified as small vessels with a distinct thin muscular coat, making them easily distinguishable from venules or lymphatics. Arterioles were counted per graticule field using the forbidden border technique[3]. On slides examined, a point corresponding to the posterior midline was positioned under the 200× objective of a microscope. The toss of a coin decided whether the field was moved to the left or right by one field of view. The same technique was used to select fields anteriorly or laterally. Numbers of arterioles per field in posterior, lateral and anterior quadrants of the subanodermal space and the IAS were recorded on a spreadsheet (Excel 4.0; Microsoft, Seattle, Washington, USA).

To estimate intraobserver variation the initial observer (J.N.L.) was blinded to the identity of the section and the number of vessels estimated in the same way as previously. Blinded counts were then compared with previous corresponding counts. To estimate interobserver variation a second independent observer (J.McG.) performed counts in the same way and the counts from each observer were compared. In each case ten sections were recounted, giving a total of 60 fields for comparison between and within observers (anterior, lateral and posterior for the subanodermal space and the IAS for each section).

Analysis of results

Comparisons between quadrants and levels were analysed using Page's L trend test for related samples[4]. This nonparametric test demonstrates whether or not the variable in question (in this case the number of arterioles per graticule field) shows a significant tendency to change in the same direction across the samples in the order that the analysis is performed (in this case anterior to posterior). Statistical comparison of variation between and within observers was made using a two-tailed, paired t test.

Results

Eight cadaveric anal canals were examined, yielding a total of 960 mounted sections, 240 of which were analysed. The block of 2 cm above the dentate line for one subject was damaged in processing and does not appear in the results. No cadaver was known to have a history of anal fissure. Mean counts at each level are given in *Table 1*. The trend of arteriolar counts per field was hypothesized to be posterior less than lateral less than anterior. Page's L trend values were calculated from mean values and are given with corresponding significance levels in *Table 2*. There was a significant trend to fewer arterioles posteriorly in the subanodermal space at all levels, and at 1 cm below and 2 cm above the dentate line in the IAS. There was no significant trend when arteriolar densities between levels 1 and 2 cm above and 1 cm below the dentate line were compared.

Using a two-tailed, paired t test to compare interobserver variation, there was no significant difference between observers for counts in the subanodermal space ($P = 0·69$) or in the IAS ($P = 0·29$). Using the same test to compare intraobserver variation, there was no significant difference between blinded counts for the subanodermal space ($P = 0·29$) or for the IAS ($P = 0·21$).

Table 1 Arteriole count per graticule field (× 200 objective) for subanodermal space and internal anal sphincter

	Submucosa			Internal anal sphincter		
Level	Posterior	Lateral	Anterior	Posterior	Lateral	Anterior
1 cm below dentate line ($n = 8$)	4·4(1·5)	6·1(1·7)	6·2(2·8)	1·3(0·6)	2·1(1·1)	1·8(0·8)
1 cm above dentate line ($n = 8$)	3·5(1·0)	5·2(1·5)	5·2(1·4)	1·4(0·7)	1·8(1·1)	1·7(0·9)
2 cm above dentate line ($n = 7$)	4·0(1·8)	5·3(1·1)	5·6(1·4)	1·1(0·5)	1·7(0·6)	1·6(0·5)

Values are mean(s.d.)

Table 2 Values of Page's L trend for the hypothesized trend towards decreasing number of arteriolar counts per graticule field from anterior to posterior

	Subanodermal space		Sphincter	
Level	L	P	L	P
1 cm below dentate line ($n = 8$)	105	< 0·05	107	< 0·05
1 cm above dentate line ($n = 8$)	106	< 0·01	97	> 0·05
2 cm above dentate line ($n = 7$)	94	< 0·01	91	< 0·05

If $P < 0·05$ the hypothesis is supported

Discussion

This study demonstrates that there is a trend towards fewer arterioles in the posterior midline of the anal canal in the subanodermal space and the IAS compared with other quadrants. It is in the posterior midline that the vast majority of anal fissures occur. Although relatively few cadavers were analysed, the method yielded a great number of sections for analysis and the technique is reproducible and reliable[3].

Klosterhalfen *et al.*[1] previously reported that there was a paucity of blood supply to the posterior midline of the anal canal in 85 per cent of cadavers examined using post-mortem angiography. It has also been demonstrated by laser Doppler flowmetry that blood flow in the posterior midline of the anal canal is less than that in other quadrants[5]. Using a different technique, the present work supports the hypothesis that the posterior midline of the anal canal is less well supplied with blood than other quadrants.

The relative paucity of arterioles in the posterior quadrant of the anal canal was observed in all eight subjects, above and below the dentate line. Anal fissures occur below the dentate line and never extend more proximally and, although common, anal fissure does not affect everyone who may have this distribution of branches of the inferior rectal artery. The IAS encircles the anal canal above and below the dentate line but exerts its greatest pressure in the distal 1–2 cm of the anal canal[6]. The treatment of chronic anal fissure depends on returning the anal resting pressure to normal either by surgery or more recently by a 'chemical sphincterotomy'. This return to normal pressure improves the blood supply to the posterior midline and results in the healing of the majority of fissures[7,8]. It may be that the poor blood supply to the posterior midline of the anal canal is further compromised by the high resting pressure of the IAS almost invariably associated with posterior anal fissure, supporting the hypothesis that anal fissure is an ischaemic ulcer[2]. Approximately 10 per cent of anal fissures in females and 1 per cent in males are in the anterior midline[9] and it may be that these lesions have a different aetiology.

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Short note

Salvage of large bowel anastomotic leaks

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Introduction

There is an extensive literature on the incidence of anastomotic leakage but advice on management generally condemns attempts to repair the leaking anastomosis[1]. Two of the authors have recently 'salvaged' leaking colorectal anastomoses and this stimulated review of their joint experience over a 6-year period.

Patients and methods

Between January 1991 and December 1996, 477 colorectal anastomoses were performed at two centres. In one unit information was collected prospectively. In the second unit operative details were recorded prospectively and supplemented by retrospective chart review. All the operations were performed using standard single-layer serosubmucosal sutured[2] or stapled techniques[3].

Results

Details of the type of anastomosis and outcome are shown in *Table 1*. There were 227 men and 250 women. Twenty-six of 65 low colorectal anastomoses were defunctioned in one centre and none of 42 in the other.

Three of the eight colorectal leaks occurred after double-stapled anastomosis and five after sutured anastomosis. There was one ileocolic leak. All nine patients required laparotomy; five of the nine leaks were salvaged. None of these nine patients died. There were ten inpatient deaths (mortality rate 2·1 per cent) due to cardiorespiratory causes (eight patients), cardiovascular accident (one) and bowel ischaemia (one).

Salvaged anastomoses

There was a small posterior dehiscence in the three stapled anastomoses that leaked. A proximal loop stoma was created in the two patients who did not already have a stoma and the defects in the anastomoses were closed with interrupted endoanal sutures. Two patients with sutured anastomoses, a low anterior resection and an ileocolic anastomosis for Crohn's disease, developed peritonitis secondary to defects in the suture line attributed to a single suture cutting through. Both were managed by creating a controlled external fistula, with a sump drain in the first patient and a Foley catheter inserted into the lumen in the second. A loop ileostomy was fashioned for the colorectal leak. None of these patients had further complications and the four stomas were subsequently closed.

Table 1 Large bowel anastomoses

Anastomosis type	*n*	Leaks	Deaths
Ileocolic	199	1 (0·5)	4 (2·0)
Colocolic	38	0 (0)	0 (0)
Colorectal			
High	108	3 (2·8)	3 (2·8)
Low	107	5 (4·7)	1 (0·9)
Ileorectal	25	0 (0)	2 (8·0)
Total	477	9 (1·9)	10 (2·1)

Values in parentheses are percentages

Abandoned anastomoses

In all four patients, three undergoing surgery for cancer and one for colovesical fistula, there was marked disruption of a sutured colorectal anastomosis over at least half the circumference due to ischaemia of the adjacent bowel. The anastomoses were all dismantled with conversion to an end stoma and closure of the distal bowel. All patients survived without complication and none has had continuity restored.

Discussion

In this study the clinical anastomotic failure rate (1·9 per cent) compares favourably with studies that comprise both elective and emergency procedures[2]. The clinical signs of leakage can develop insidiously and dehiscence must be confirmed or refuted with a water-soluble enema as soon as clinical suspicion is raised. The conventional management of a clinical leak with peritoneal contamination is to abandon the anastomosis with exteriorization of one or both ends of the bowel. Although subclinical leaks detected only on routine contrast enema are managed conservatively, inappropriate expectant management of a clinical leak with protracted non-operative treatment may be responsible for high mortality and morbidity rates.

Salvage of anastomoses has generally been condemned in the surgical literature[1]. However, in this study the majority of leaks were salvaged, three by direct suture and two by creating a controlled external fistula, with no deaths due to leakage. The key to salvage with a good outcome is early diagnosis with rapid intervention and selection of appropriate operative treatment.

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Leucocyte count and C-reactive protein in the diagnosis of acute appendicitis

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Background: The aim of the present work was to study the preoperative leucocyte counts and C-reactive protein (CRP) values in three groups of patients operated on for a clinical suspicion of acute appendicitis with different findings at appendicectomy: an uninflamed appendix, uncomplicated acute appendicitis or complicated acute appendicitis. In particular, patients with acute appendicitis but a normal leucocyte count and CRP level were sought.

Methods: In this retrospective study, the mean preoperative leucocyte count and CRP value in 100 consecutive patients with an uninflamed appendix (group A), in 100 consecutive patients with uncomplicated acute appendicitis (group B) and in 100 consecutive patients with complicated acute appendicitis (group C) were calculated. The numbers of patients with (1) both values normal, (2) only leucocyte count raised, (3) only CRP level raised and (4) both values raised were calculated in each of the three groups.

Results: The increase in leucocyte count was an early marker of appendiceal inflammation, whereas the CRP value increased markedly only after appendiceal perforation or abscess formation. Group A (uninflamed appendix) contained 24 patients in whom both values were normal. Neither group B (uncomplicated acute appendicitis) nor group C (complicated acute appendicitis) contained any patient with both values in the normal range.

Conclusion: Acute appendicitis is very unlikely when both the leucocyte count and CRP value are normal.

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Introduction

The diagnosis of acute appendicitis is still difficult and very probably the most common diagnostic problem in clinical surgery. The accuracy of diagnosis of acute appendicitis has improved only marginally in recent decades[1–3]. The classic triad of a history compatible with acute appendicitis, pain at McBurney's point and leucocytosis has a diagnostic accuracy rate of less than 80 per cent and, even when radiological techniques such as ultrasonography, computed tomography or radionuclide scanning are included, the accuracy does not usually reach 90 per cent[3–7]. In a recent study, the accuracy of diagnosis of acute appendicitis was 79 per cent at this hospital[6]. In particular, the question of how to avoid unnecessary appendicectomies still remains.

Many clinicians have encountered patients who have been operated on for a clinical suspicion of acute appendicitis, even though the preoperative leucocyte count and C-reactive protein (CRP) value were normal. It seems that, in these cases, an uninflamed appendix is often found at appendicectomy. The purpose of the present work was to study the preoperative leucocyte counts and CRP values in three groups of patient operated on for a clinical suspicion of acute appendicitis with different findings at appendicectomy: an uninflamed appendix, uncomplicated acute appendicitis or complicated acute appendicitis. In particular, patients with acute appendicitis but a normal leucocyte count and CRP value were sought.

Patients and methods

All patients were operated on during the years 1993–1997. This hospital is a 1200-bed teaching hospital serving an area of 435 000 inhabitants in south-western Finland. Three groups of patients were included in the current retrospective study.

Group A comprised 100 consecutive patients operated on for a clinical suspicion of acute appendicitis but who had an uninflamed appendix at appendicectomy (recruitment time 42 months). Most patients in this group suffered from non-specific abdominal pain but a number of inflammatory and non-inflammatory diseases including urinary tract infection, mesenteric lymphadenitis, acute diverticulitis and rupture of ovarian cyst were also found. The mean age of the patients in this group was 32 (range 3–78) years; there were 62 female and 38 male patients.

Group B comprised 100 consecutive patients operated on for a clinical suspicion of acute appendicitis who had an uncomplicated acute appendicitis found at appendicectomy (recruitment time 12 months). The mean age of the patients in this group was 32 (range 7–71) years; there were 45 female and 55 male patients.

Group C comprised 100 consecutive patients operated on for a clinical suspicion of acute appendicitis in whom complicated acute appendicitis (perforated appendix or periappendicular abscess) was confirmed (recruitment time 48 months). The mean age of the patients in this group was 41 (range 3–83) years; there were 33 female and 67 male patients.

The diagnosis was confirmed in all cases by histological examination of the appendix. Since some degree of superficial inflammation may follow drainage of exudate into the appendix from a more proximal lesion such as ileitis, the histological diagnosis of acute appendicitis required involvement of the muscularis of the appendix. In all cases, at least two transverse sections from the proximal half of the appendix and one longitudinal section from the distal half were studied.

Blood samples were obtained from the patients on admission to hospital. In those few patients who underwent appendicectomy only after period of observation, an additional blood sample taken immediately before operation was used for laboratory measurements. Leucocyte count was determined by an electronic cell counter (Coulter Counter T 890; Coulter Electronics, Hialeah, Florida, USA). The concentration of CRP was measured by immunoturbidimetry (Hitachi 717; Hitachi, Tokyo, Japan). The upper limit of the reference interval for leucocyte count was 9×10^9 per litre for females and 10×10^9 per litre for males; that for CRP was 10 mg/l. The results of the laboratory tests were obtained within 1–2 h and the surgeon on duty was thus aware of both laboratory results before a decision was made to operate.

Each of the three patient groups was divided into four subgroups according to the preoperative leucocyte counts and CRP values of the patients: subgroup 1, both leucocyte count and CRP value normal; subgroup 2, leucocyte count raised and CRP value normal; subgroup 3, CRP value raised and leucocyte count normal; and subgroup 4, both leucocyte count and CRP value raised. The numbers of patients in these four subgroups were calculated for each of the three patient groups.

Data are presented as mean(s.e.m.). An unpaired, two-sided Student's *t* test was used for comparison of laboratory values between groups A–C.

Results

The mean(s.e.m.) values for leucocyte count and CRP concentration are shown in *Table 1*. The mean leucocyte count was significantly higher ($P < 0{\cdot}001$) in patients with uncomplicated acute appendicitis (group B) and those with complicated acute appendicitis (group C) than in those with an uninflamed appendix (group A).

The mean CRP value of patients with uncomplicated acute appendicitis (group B) did not differ from that of patients with an uninflamed appendix (group A) but in group C the level was significantly higher ($P < 0{\cdot}001$) than that in group A or group B.

Fig. 1 shows the division of the three patient groups into the four subgroups according to preoperative leucocyte counts and CRP levels. In patients with an uninflamed appendix at appendicectomy, all four subgroups were fairly equally represented. In patients with uncomplicated acute appendicitis, the majority of the patients fell into two subgroups: raised leucocyte count and normal CRP level, or both values raised. In patients with complicated acute appendicitis, the vast majority of the patients had both values raised. The most conspicuous finding was that all patients with both values in the normal range had a non-inflamed appendix. In this group of 24 patients with normal laboratory values and negative appendicectomies, there were 20 patients with non-specific abdominal pain, two with urinary tract infection and two with rupture of an ovarian cyst. None of these 24 patients would have needed surgical intervention.

Table 1 Leucocyte count and C-reactive protein value in patients with a clinical suspicion of acute appendicitis who underwent appendicectomy

	Leucocyte count ($\times 10^9$ per litre)	CRP (mg/l)
Group A (*n* = 100)	10·9(0·4)	32(5)
Group B (*n* = 100)	14·5(0·4)	31(4)
Group C (*n* = 100)	14·3(0·4)	99(7)

Values are mean(s.e.m.) Group A, uninflamed appendix; group B, uncomplicated acute appendicitis, group C, complicated acute appendicitis. CRP, C-reactive protein

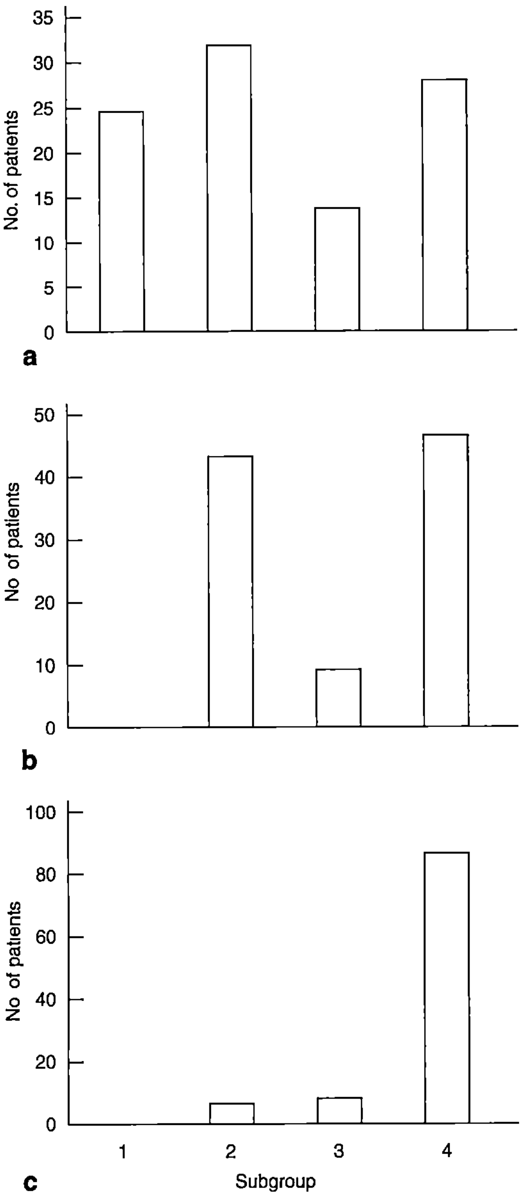

Fig. 1 Division of patients with **a** an uninflamed appendix, **b** uncomplicated acute appendicitis and **c** complicated acute appendicitis into four subgroups according to preoperative leucocyte count and C-reactive protein (CRP) values. Subgroup 1, both values normal; subgroup 2, only leucocyte count raised; subgroup 3, only CRP raised; subgroup 4, both values raised

Discussion

In the present patient population, there were 24 patients who had been operated on for a clinical suspicion of acute appendicitis, even though the preoperative leucocyte count and CRP value were normal. Interestingly, all of these 24 patients belonged to the group who did not have appendicitis ($n = 100$). In all patients with acute appendicitis ($n = 200$), either leucocyte count or CRP value, or both, were above normal limits. Thus, although there was a clinical suspicion of acute appendicitis, normal leucocyte count and CRP value excluded acute appendicitis with a predictive value of 100 per cent in the present study. In these patients, 24 per cent of unnecessary appendicectomies would have been avoided by trusting in this finding. None of this group of 24 patients would have needed surgical intervention. Based on the present study, appendicectomy is not recommended for patients with a normal leucocyte count and CRP value, even when acute appendicitis is suspected clinically. These patients should be treated by careful clinical observation, and additional leucocyte count and CRP measurements. If clinical symptoms and signs of acute appendicitis continue and leucocyte count and/or CRP value increases above the upper limit of the reference interval, the patient should undergo laparoscopy/appendicectomy. Otherwise, continued observation is recommended.

In the present study, leucocyte count was a better laboratory test than CRP value in diagnosing uncomplicated acute appendicitis, whereas CRP value was superior to leucocyte count in reflecting appendiceal perforation or abscess formation. These results are in accordance with earlier reports[6,8–10]. Previous and present results suggest that increased leucocyte count is usually the earliest laboratory test to indicate appendiceal inflammation. Only during protracted inflammation are levels of acute-phase reactants such as CRP increased. The leucocyte count does not, however, increase any more during protracted inflammation such as in the case of appendiceal perforation or abscess formation, as reported earlier[6,9] and confirmed in the present study.

The majority of the present patients with an uninflamed appendix at appendicectomy were women, as was expected owing to gynaecological disorders which mimic acute appendicitis[11]. In women, the diagnostic accuracy in acute appendicitis is usually as low as 60–70 per cent[1,5,6,12]; in women of childbearing age the results are even less satisfactory with the diagnostic accuracy rate usually lower than 60 per cent[1,12]. Laparoscopy was recently recommended for all young women with right lower abdominal pain: it usually gives a precise diagnosis and reduces the rate of negative appendicectomies[13].

In conclusion, the increase in leucocyte count is a very early marker of appendiceal inflammation, whereas CRP level usually increases markedly only after appendiceal perforation or abscess formation. Acute appendicitis seems to be very unlikely in a patient with a normal leucocyte count and CRP value, even if clinical symptoms and signs indicate acute appendicitis.

Acknowledgements

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Laparoscopic surgery in the treatment of colonic polyps

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Background: Benign colonic polyps that are impossible to remove with the aid of the flexible colonoscope because of their size or location must be removed surgically.
Methods: Twenty patients with colonic adenomatous polyps that could not be resected by colonoscopy because of size or difficult location ($n = 18$) or polyps in combination with diverticulitis ($n = 2$) underwent polyp removal through a small 'assisted' incision in the abdominal wall using a standard 'dissection-facilitated' laparoscopic approach to the affected colonic segment.
Results: In six patients the polyp was removed through a colotomy, in three through a limited resection (two ileocaecal and one limited sigmoid resection) and in 11 through a standard colectomy (four right hemicolectomy, one left hemicolectomy, four sigmoid and two anterior resections) because of suspicion of cancer. In only one patient could the polyp not be found during laparoscopy, resulting in a second conventional surgical intervention. In four patients carcinoma was diagnosed in the specimen.
Conclusion: Precise preoperative localization of the polyp and the use of dissection-facilitated laparoscopic colonic surgery make laparoscopic removal of benign colonic polyps an alternative to an open procedure.

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Introduction

The standard treatment of benign colonic polyps is resection using a diathermy wire loop. Large polyps (greater than 2·5 cm) can be removed by colonoscopy if adequate visualization of the pedicle is possible and the head can be ensnared. Sessile polyps, however, can be removed piecemeal but this technique is not advised for ulcerating polyps[1]. The experience of the endoscopist determines the size and the nature of lesions that the surgeon is willing to approach. Because of their difficult location or size, some polyps are impossible to remove at flexible colonoscopy and must be removed surgically[1,2]. Developments in laparoscopic colonic surgery have contributed to the application of this approach to the resection of colonic polyps[3–14]. The laparoscopic approach has brought with it two technical challenges: first, the localization of the polyp and, second, its proper surgical extirpation. Depending on the shape of the polyp, its size and location, proper extirpation can be performed through a colotomy (pedunculated or small sessile polyps), a limited colectomy (large sessile polyps) or an oncological resection in case of suspicion of carcinoma. This paper describes experience with the laparoscopically assisted removal of 20 colonic polyps considered before operation to be benign.

Patients and methods

From November 1991 to December 1997, 129 laparoscopic colonic interventions were performed for colonic conditions diagnosed before operation as 'benign', 20 of which were colonic polyps irresectable by colonoscopy. Seventeen patients were diagnosed as having adenomatous polyps by biopsies taken during colonoscopy and in a further three patients, despite visualization, neither biopsy nor excision could be performed because of the difficult location. Even though policy was to perform laparoscopic resection only after colonoscopic localization, difficulty in finding a right-sided polyp in one patient resulted in the use of a barium enema for anatomical localization in the last 11 patients. Barium enema imaging suggested malignancy in three of these patients.

In all cases the preoperative decision to approach the lesions as benign polyps and not as cancer was made on both histological and colonoscopic appearances.

Reasons for referral to surgery were: (a) difficult location (six caecal, four in the hepatic flexure and one in the transverse colon); (b) size (one in the descending colon, four in the sigmoid and two in the proximal rectum); and (c) polyps in the sigmoid found after an initial episode of acute diverticulitis (two patients).

General laparoscopic technique

According to the preoperative localization, the affected colonic segment was approached by the so-called laparoscopic 'dissection-facilitated' procedure. In this procedure the entire affected colonic segment is mobilized at laparoscopy, exteriorized through a well placed small incision, subsequently resected and anastomosed[15]. A standard approach published elsewhere[16,17] was used. Depending on the preoperative localization, complete mobilization of standard colonic segments (right colon, transverse colon, left colon, sigmoid colon and proximal rectum) with their corresponding mesentery was performed. If the exterior aspect of the corresponding segment of the colon showed changes typical of cancer (invasion of the serosa and rigidity), the lesion was approached as a carcinoma. Once the proper segment had been dissected free it was exteriorized through a well protected, assisted periumbilical incision of 7 cm. With the exception of the first two patients in whom a lower right incision was performed, the periumbilical approach was used for all parts of the colon except for polyps located in the sigmoid colon or proximal rectum for which a Pfannenstiel incision was preferred.

Specific laparoscopic technique

After exteriorization of the colonic segment, evaluation of the polyp by palpation was performed. If on palpation the polyp felt completely soft and its size was less than 2·5 cm, resection was performed through a longitudinal colotomy through a tenia. A submucosal injection of saline and subsequent radical extirpation by means of diathermy with a 1-cm margin followed. Frozen-section examination determined the exact diagnosis and free margins. The colotomy was closed transversely in two layers. If on palpation the polyp felt soft but was larger than 2·5 cm, a limited colonic resection and frozen-section study was carried out. If there was any suspicion of cancer (during laparoscopic inspection or at palpation of the exteriorized colonic segment) a standard laparoscopic oncological resection was performed. If on exteriorization the polyp could not be clearly palpated, intraoperative endoscopy was called for. Colonoscopy was used in three patients to find polyps in the transverse, descending and sigmoid colon, and endoluminal endoscopy (with the laparoscope and the corresponding cannula of 10 mm introduced through the appendicular basis) to localize a polyp in the hepatic flexure. In the endoluminal technique, intraluminal pressure should not exceed 8 mmHg to prevent the risk of perforation.

Results

All 20 patients, 13 men and seven women with a mean age of 63·2 (range 45–83) years, were approached laparoscopically. In one patient with a polyp localized before operation in the caecum which could not be found after exteriorization of the right colon, conversion to laparotomy was not made, and the removal was postponed until a better localization procedure had been performed. After a colonoscopy and barium enema the patient underwent a conventional right hemicolectomy for a polyp localized distal to the hepatic flexure.

A further nine polyps were localized in the right colon. Three polyps were removed through a colotomy in the caecum, one by a colotomy in the hepatic flexure, two by ileocaecal resection and the other three by means of a right hemicolectomy.

One polyp found in the transverse colon was removed by colotomy. One polyp localized in the descending colon and suspected of being cancerous was resected by a left hemicolectomy.

In eight patients, polyps were found in the sigmoid colon and proximal rectum. After mobilization, the specimens were exteriorized in four patients through a left lower abdominal muscle-splitting incision and in the other four through a Pfannenstiel incision. One polyp was removed by means of a colotomy, another by limited sigmoid resection, four by sigmoid resection (in two patients because of concomitant diverticulitis) and in the last two patients by anterior resection. With the exception of the patient who underwent a second surgical intervention, no conversions to laparotomy were performed in this series.

In four patients a carcinoma was found, Dukes stage B1 in three and B2 in one. All resections were considered as radical. The remaining patients had either a tubulovillous adenoma (11 patients), villous adenoma (one), hyperplastic polyps (two), invaginated appendix stump with initial changes of adenomatous tissue (one) or a large lipoma in the ascending colon (one). The diameter of the tumours ranged from 3 to 6 cm and the adenomatous polyps varied from 1·7 to 5·5 cm. The two resected hyperplastic polyps were localized in the caecum (1·5 cm) and the sigmoid (5 cm).

The mean length of postoperative hospital stay was 5 (range 3–16) days. No major complications occurred. One patient had a wound infection and another a urinary infection. Follow-up included outpatient colonoscopy (except in patients with hyperplastic polyps or lipoma). In two of 12 patients benign adenomatous polyps measuring 5 mm were found in the sigmoid colon and were extirpated.

Discussion

The standard treatment for colorectal benign polyps is colonoscopic removal using a wire loop[1]. This treatment has a low complication rate and is currently performed on an outpatient basis. Pedunculated lesions are easier to remove than sessile ones. Limitations of this treatment are the ability of the endoscopist to remove a large polyp (greater than 2 5 cm) or to extirpate a lesion in a difficult location such as the hepatic flexure or caecum[1]. These polyps require surgical removal. The risk of invasive carcinoma being harboured in a colorectal adenoma can be adequately predicted endoscopically on the basis of two variables: size and location. This risk increases with adenoma size irrespective of anatomical location. In small polyps (between 5 mm and 1·5 cm) the risk of cancer is 2 per cent in the rectum and less than 1 per cent in the rest of the colon. Between 1·6 and 2·5 cm, these values increase to 30 and 12 per cent. If the size of the polyp is larger than 2·5 cm, values are 51 and 34 per cent respectively[2].

These risk factors for invasive carcinoma influence surgical strategy. Polyps less than 2·5 cm and appearing soft on palpation may be approached by a colotomy followed by frozen-section examination. Soft polyps larger than 2·5 cm should be resected initially by a limited resection (and frozen-section study), and lesions suspected for cancer should be approached as carcinoma and resected oncologically. The results of this series confirm the adequacy of this strategy when employing the laparoscopically assisted approach: all carcinomas had been suspected during the laparoscopic phase of the operation or during palpation of the exteriorized colonic segment. The finding of invasive carcinoma in four of 20 patients is in concordance with the literature for surgically removed polyps[2].

Several studies on laparoscopic colonic resection have reported a small proportion of patients in whom the indication for surgery was polyps[6,8] and this may be one of the best indications for laparoscopic colonic surgery[7]. In the case of inaccessible polyps, Smedh *et al.*[14] mobilized the corresponding colonic segment by laparoscopy, gaining access for the flexible colonoscope. For colonoscopic extirpation of difficult or large polyps, Averbach *et al.*[13] used laparoscopy as an observational tool to ensure that the colonoscopist did not perforate the wall of the colon during polyp removal.

Preoperative localization methods, such as an India ink tattooing[18] injected 1 day before the operation and laparoscopic ultrasonography of the colon, have been used with good results. At laparotomy, Botoman *et al.*[18] found the tattoo in 11 of the 14 marked patients. They advised using this technique in flat colonic cancer and for previously snared malignant polyps that cannot be palpated during operation. Systematic tattooing of polyps complementary to colonoscopy and barium enema may increase their preoperative localization, especially if the polyps are small and flat. In the present authors' experience the major problem is not localization of the polyp during the surgical procedure, but rather the attainment of an adequate approach to excise it. A good preoperative localization procedure, such as double-contrast colonic enema, followed by adequate mobilization and exteriorization of the affected colonic segment will permit the surgeon to make a decision concerning the extent of resection. Special problems are associated with polyps located in the sigmoid–rectum transition area and complicate the choice of approach. Even if transanal endoscopic microsurgery is possible for adenomas located on the posterior wall up to about 18 cm from the anus, excision at the anterior wall above 10 cm is not advisable because beyond this point the abdominal cavity can be opened during the dissection[19]. Therefore, only polyps located higher up should be approached laparoscopically. To aid the decision, sigmoidoscopy should be repeated before operation because the distance measured by the flexible endoscope is not always accurate. Nowadays the introduction of endostaplers through a bivalve speculum permits the resection of small polyps (up to 2·5 cm) in the entire circumference of the rectum as far as 15 cm from the anus[20].

In conclusion, polyps that cannot be removed at colonoscopy (because of size or location) may be approached laparoscopically. Conservative or oncological resection is determined by palpation of the polyp and its size.

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Original article

Red blood cells inhibit tumour cell adhesion to the peritoneum

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Background: Perioperative blood transfusion has been associated with increased tumour recurrence and poor prognosis in colorectal cancer. Blood loss in the peritoneal cavity might be a tumour-promoting factor for local recurrence. The aim of this study was to investigate whether blood in the peritoneal cavity affects local tumour recurrence.
Methods: In an established *in vivo* rat model the effect of 1·5 ml syngeneic whole blood on tumour cell adhesion and tumour growth was investigated. In the same model the effect of 1·5 ml pure red blood cell (RBC) concentrate and 1·5 ml RBC-derived substances on tumour cell adhesion was studied. In an established *in vitro* model the effect of increasing numbers of RBCs ($0–250 \times 10^6$) on tumour cell adhesion and tumour growth was assessed.
Results: Both the presence of blood and RBC concentrate in the peritoneal cavity prevented tumour cell adhesion *in vivo* (overall $P \leq 0{\cdot}001$ and $P \leq 0{\cdot}05$ respectively), rather than promoting adherence. RBC concentrate and RBC-derived substances had a comparable inhibitory effect on tumour cell adhesion. In *in vitro* studies RBCs inhibited tumour cell adhesion but not tumour growth.
Conclusion: RBC-derived factors prevent tumour cell adhesion to the peritoneum, and consequently tumour recurrence.

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Introduction

Peroperative blood transfusion, irrespective of whether it is allogeneic or autologous, is associated with enhanced tumour recurrence and poor prognosis in patients with colorectal cancer[1–3]. In the study by Busch *et al.*[2], the association between recurrent disease and blood transfusion appeared to exist only for the incidence of local recurrence and not for the incidence of distant metastases. Furthermore, it was concluded that the circumstances necessitating transfusion were the real determinants of prognosis[2]. Conditions leading to blood transfusion are the location and extent of the primary tumour, skill of the surgeon and length of operation. Blood loss in the peroperative period, however, is the most common reason for transfusion.

The effect of blood loss on tumour recurrence has been studied extensively in experimental animal models. The results of these studies are controversial and report both stimulatory and inhibitory effects on tumour growth, irrespective of whether blood transfusion is given[4–6].

Based on the clinical observation that conditions leading to transfusion are the real determinants of prognosis, as well as the experimental results indicating that blood loss itself is an important factor influencing tumour growth, it was hypothesized that local blood loss, i.e. in the peritoneal cavity, might be a factor influencing local tumour recurrence. The present paper reports an *in vitro* and *in vivo* study investigating the effect of blood and blood products on the establishment of intraperitoneal tumour recurrence.

Materials and methods

Animals

Inbred rats of the WAG strain were obtained from Harlan-CPB (Zeist, The Netherlands) and kept under standard conditions. The experimental protocol adhered to rules laid down by the Dutch Animal Experimentation Act and was approved by the Committee for Animal Research of the Erasmus University Rotterdam.

Tumour cell line

The syngeneic CC531 colon carcinoma was induced in WAG/Rij rats by 1,2-dimethylhydrazine. A cell line was established from this carcinoma and maintained by serial passage after trypsinization in culture medium[7,8]. CC531 cells were cultured in RPMI 1640 medium supplemented with 5 per cent fetal calf serum, L-glutamine 200 mmol/l, penicillin 5000 units/ml and streptomycin 5000 units/ml. All supplements were obtained from Gibco, Paisley, UK. Before use, cells were trypsinized (10 min at 37 °C), centrifuged (5 min at 700*g*), resuspended in RPMI 1640 and counted. Viability was measured by trypan blue exclusion and always exceeded 90 per cent.

Blood products

WAG rats were exsanguinated by cardiac puncture. Red blood cell (RBC) concentrate was obtained by centrifugation of blood and resuspending the pelleted RBCs in RPMI medium to the original volume. Using this suspension, RBC content was collected by lysing RBCs in liquid nitrogen. The resulting homogenate was divided into 1·5-ml aliquots and centrifuged at 10 000 r.p.m. for 15 min to pellet cell fractions.

In vivo experiments

Operative procedure and tumour scoring

Under ether anaesthesia a laparotomy was performed followed by peritoneal inoculation of 10^6 CC531 tumour cells. The abdomen was closed in one layer with silk 2/0 sutures (Braun, Uden, The Netherlands). Three weeks after operation the rats were killed and tumour establishment was scored at multiple intraperitoneal sites. The scoring ranged from 0 to 5 per site, according to the peritoneal cancer index described by Steller[9].

Experimental design

In the first experiment, the effect of 1·5 ml syngeneic whole blood on intraperitoneal tumour recurrence was determined. The control group received 1·5 ml phosphate-buffered saline (PBS). Both groups consisted of ten rats.

In the second experiment, tumour cells were allowed to adhere before performing a relaparotomy after 24 h and adding 1·5 ml whole blood. The control group received PBS. Both groups consisted of eight rats.

In the third experiment, the effect of 1·5 ml RBC concentrate on tumour establishment was evaluated. The control group received 1·5 ml PBS; both groups consisted of ten rats.

In the last experiment, a distinction was made between RBCs and RBC contents using the supernatants derived from 1·5 ml lysed RBC concentrate. Both groups comprised nine rats.

In vitro experiments

Mesothelial cell culture

Mesothelial cells were isolated from the small bowel mesentery of rats and identified immunohistochemically as described before[10]. Mesothelial monolayers were established in 24-well plates (Costar, Badhoevedorp, The Netherlands), precoated with collagen type I (Boehringer Mannheim, Mannheim, Germany).

Experimental design

RBCs ranging in concentration from 10 to 250 × 10^6 were added to the wells coated with mesothelium or collagen type I. In the first experiment RBCs and 40 000 CC531 tumour cells were added simultaneously. In the second experiment the effect of RBCs on tumour growth was evaluated by leaving CC531 cells to adhere overnight, before adding RBCs. To determine a potential direct toxic effect, RBCs were added to a mesothelial monolayer. After 48 h, the plates were collected by washing away superfluous non-adherent cells and kept at −20°C for DNA analysis.

DNA analysis

The total DNA content of each well was measured using the bisbenzimide fluorescent dye (Boehring Diagnostics, La Jolla, California, USA) as described previously by Hofland *et al.*[11]. The DNA measured represents the total amount of cells per well.

Statistical analysis

Statistical analysis was performed using the Kruskal–Wallis analysis of variance to determine overall differences followed by the Mann–Whitney *U* test to compare differences between groups.

Results

In vivo experiments

Effect of whole blood on peritoneal tumour take

Significant differences in tumour take at all peritoneal sites scored were found between the control and experimental groups. Adding 1·5 ml blood to the peritoneal cavity simultaneously with tumour cells inhibited the take of tumour cells (*Table 1*).

When blood was injected after the CC531 tumour cells had adhered, however, no significant differences in tumour take could be detected (results not shown). This indicates that the protective effect of blood is based on preventing tumour cell adhesion rather than affecting tumour growth.

Effect of red blood cells on peritoneal tumour take

Adding 1·5 ml pure RBC concentrate together with tumour cells produced a similar effect to that obtained when whole blood was used. At all scored peritoneal sites there was significantly less tumour take when RBC concentrate was added simultaneously with 10^6 CC531 tumour cells (*Table 2*).

When comparing the effect of RBCs with RBC contents, no differences in tumour take could be scored (results not shown). These results indicate that inhibition of tumour cell adhesion to the peritoneum can be attributed to the content of RBCs rather than the RBCs as a whole.

In vitro experiments

RBCs in large amounts did not have a direct toxic effect on the mesothelial monolayer. A significant inhibition of tumour cell adhesion was observed, irrespective of adherent background, after adding 50 × 10^6 RBCs or more ($P < 0·05$). No further inhibitory effect was seen after adding more than 100 × 10^6 RBCs (*Fig. 1*). When CC531 cells were left to adhere before adding the RBCs no difference in adherence could be measured (data not shown). These *in vitro* results indicate, as the *in vivo* results, that the observed inhibition of tumour establishment by RBCs is based on impeding tumour cell adhesion rather than affecting tumour growth.

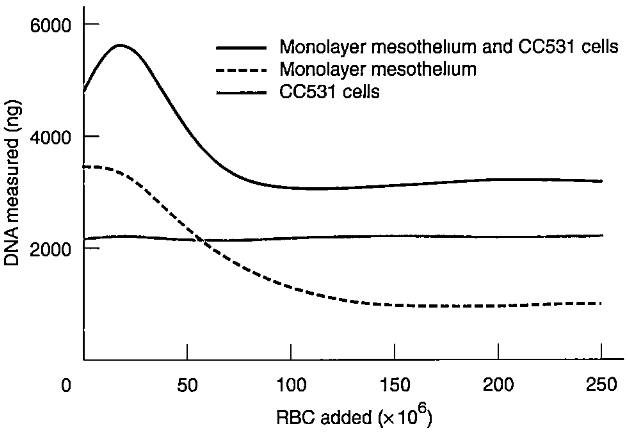

Fig. 1 Tumour cell adhesion represented by total DNA measured. Values are mean(s.d.) ($n = 4$)

Table 1 Effect of whole blood in the peritoneal cavity on local tumour take

Abdominal site	1·5 ml PBS (n = 10)	1·5 ml blood (n = 10)	P*
Subcutis	3 (2–5)	1 (0–3)	0·001
Mesentery	2 (1–3)	0 (0–1)	< 0·0001
Kidney	3 (1–5)	1 (0–1)	0·0001
Liver	2 (1–3)	0 (0–1)	0·0001
Omentum	3 (2–5)	0 (0–1)	< 0·0001
Retroperitoneum	2 (0–2)	0 (0)	0·0002

Values are median (range) peritoneal cancer index score PBS, phosphate-buffered saline. *Mann–Whitney U test

Table 2 Effect of red blood cells in the peritoneal cavity on local tumour take

Abdominal site	1·5 ml PBS (n = 10)	1·5 ml RBCs (n = 10)	P*
Subcutis	5 (4–5)	1 (0–3)	< 0·001
Mesentery	2 (1–4)	0 (0–4)	0·002
Kidney	3 (2–5)	1 (0–5)	0·004
Liver	2 (2–4)	0 (0–2)	< 0·001
Omentum	5 (4–5)	0 (0–5)	< 0·001
Retroperitoneum	1 (0–3)	0 (0–4)	0·05

Values are median (range) peritoneal cancer index score. PBS, phosphate-buffered saline, RBC, red blood cell. *Mann–Whitney U test

Discussion

Local or regional tumour recurrence, or both, may be a result of residual microscopic disease, direct extension into adjacent organs or intraoperative implantation of exfoliated tumour cells. In the latter process, tumour cells shed into the peritoneal cavity survive and grow into established tumours. Adjuvant measures to kill the exfoliated tumour cells may prevent this mode of recurrence.

The observation that the presence of RBCs in the peritoneal cavity could impede tumour establishment was reason enough to explore this phenomenon. There were primarily three hypotheses proposed for the mechanism of this effect, the first being a growth-limiting effect. The *in vitro* studies demonstrated that there was no decline in total DNA after 48 h caused by RBCs, i.e. no decline in tumour cell number, once the tumour cells had adhered. Furthermore, after adhesion of CC531 cells *in vivo* a growth-inhibiting effect could not be detected. Both experiments prove that RBCs do not inhibit tumour growth, and that the inhibition of tumour take by RBCs takes place at the point of tumour cell adhesion.

The second hypothesis was that tumour cell adhesion could be impeded by mechanical inhibition. Although in the *in vivo* studies this hypothesis was less likely to be relevant, in the *in vitro* studies a significant inhibition of tumour cell adhesion was seen after adding 50×10^6 or more RBCs. This is at least 1250 times more RBCs than tumour cells which may impede tumour cell adhesion through mechanical inhibition.

The third hypothesis was accredited to an unknown function of RBCs, which could be executed by either the RBC membrane or contents. It was demonstrated that the latter produced a similar inhibitory effect on tumour establishment to that of intact RBCs, indicating that mechanical inhibition by an excess of RBCs was not relevant and so the inhibition of tumour cell adhesion to the peritoneum could be attributed to the content of RBCs rather than intact RBCs.

Other than oxygen transporters, RBCs are known to contain several antioxidant protectors. These scavengers catalyse or accelerate the dissociation of oxygen free radicals which play a fundamental role in cellular injury in a wide variety of pathophysiological processes. Following abdominal surgery, the most likely source of these free radicals is a rapid influx of neutrophils and macrophages, recruited to the abdominal cavity as a result of surgical trauma or inflammation[12,13]. The purpose of these reactive cell products is to destroy invading organisms and damaged tissue.

Excessive or inappropriate production of free radicals is associated with morbidity and death after peritoneal trauma and inflammatory disease[14,15]. Diminution of peritoneal trauma by scavengers affecting free radical-mediated injury might contribute to the prevention of implantation of spilled tumour cells.

The results of the present experiments indicate a possible relation between scavengers carried by RBCs and prevention of free radical-mediated injury. In previous *in vivo* studies a significant correlation between the extent of peritoneal trauma and the degree of tumour implantation was shown[16]. The evidence to date supports an effector role of RBCs in actively preventing tumour cell adhesion to the peritoneum, resulting in less tumour take. Additional studies are required to determine which of the three scavengers that are transported in the cytoplasm of RBCs (glutathione peroxidase, catalase and superoxide dismutase) bring about this effect.

The potential for clinical application of scavengers to modify free radical injury, and so inhibit establishment of peroperatively spilled tumour cells, may lead to new therapeutic approaches for the prevention of locoregional recurrence.

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Original article

Comparison of two closure techniques for the repair of experimental colonic perforations

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Background: Primary repair of penetrating wounds of the colon is gaining increasing acceptance in surgical practice. This study compared two techniques for the repair of experimental colonic perforations in the presence of peritonitis.
Methods: Multiple colonic perforations were created in the colon of 24 pigs. Following a 6-h delay the perforations were closed either by local excision and suture or by skin staples applied to the seromuscular layers of the colon. The repairs were assessed biomechanically and histologically for up to 14 days after surgery.
Results: All animals had diffuse peritonitis at the time of colonic repair. Stapled repairs were completed significantly faster than sutured repairs (mean(s.d.) 4·8(1·6) *versus* 30·7(4·0) min, $P < 0{\cdot}001$). Biomechanical evaluation of repairs revealed no significant differences between the two techniques. Histological examination of repairs closed by staples demonstrated more advanced healing compared with suture closure, on the basis of tissue apposition and inflammatory changes.
Conclusion: Experimental colonic injuries may be treated successfully by primary repair in the presence of peritonitis. The use of skin staples for repair does not appear to prejudice colonic wound healing.

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Introduction

Penetrating abdominal trauma, especially that caused by ballistic weapons, is often associated with multiple abdominal injuries, including colonic perforation[1]. Although these injuries occur in both civilian and military casualties, their management is often very different[2,3]. Results from clinical trials involving civilian patients have recently led to the suggestion that all colonic wounds should be managed by primary repair. There are published reports of colonic injuries having been managed successfully either by closure of a wound or by excision and anastomosis, without forming a proximal defunctioning colostomy. The surgical techniques employed have included sutures or proprietary intestinal staples[4–6].

Skin staples applied to the seromuscular layers of the colon may provide an alternative method to allow rapid closure of defects, facilitating a reduction in operating time, without the requirement for specialist equipment. The technique has been used for performing anastomoses of the small intestine and colon, both experimentally[7–9] and clinically[10]. It has also been employed for the immediate closure of experimental colonic perforations[11]. Fraser[10] reported the use of this technique for intestinal anastomosis in three patients with peritonitis, but there are no experimental studies of its use in the presence of peritonitis. This study evaluated the healing of experimental colonic perforations, produced by ballistic injury, repaired either by excision and suture or by inversion of wound edges with skin staples, in the presence of bacterial peritonitis.

Materials and methods

All procedures were authorized under the Animals (Scientific Procedures) Act 1986. Twenty-four female Large White pigs were used (mean(s.d.) weight 49·3(5·7) kg). General anaesthesia was induced by inhalation of halothane–oxygen–nitrous oxide and maintained by intravenous infusion. Under aseptic conditions a midline laparotomy was performed and a section of the right (spiral) colon was mobilized and suspended above the laparotomy wound. Perforations, each encompassing an entry and an exit wound, were produced at 10-cm intervals along the colon, using steel fragments (3·2 mm in diameter, mass 200 mg) fired from a laser-sighted barrel.

All wounds were measured using a ruler applied to the serosal surface of the colon. Once six perforations (i.e. 12 wounds) had been created, the colon was returned to the abdomen, and the laparotomy wound closed.

After 6 h the abdomen was re-explored. The colon was exteriorized following peritoneal lavage. In each animal six wounds were closed by local excision and suture with 2/0 polyglactin 910 (Vicryl; Ethicon, Edinburgh, UK) using a simple interrupted single-layer serosubmucosal technique. The remaining six wounds were closed by apposition and inversion of wound edges by placement of staples (Multifire-35 Premium; AutoSuture, US Surgical, Norwalk, Connecticut, USA) through the serosal surface, incorporating the seromuscular layers[10]. The closed dimensions of each staple were 4·7 × 3·5 mm and they were inserted approximately 6 mm apart.

Peritoneal lavage was repeated following colonic repair, and the laparotomy wound closed. Buprenorphine was administered before recovery, with repeat dosing according to clinical response. Animals received 600 mg penicillin and 2 g piperacillin by intramuscular injection every 6 h for 5 days, starting 1 h after colonic wounding. This was based on current military medical antibiotic policy[12].

Animals in group 1 (*n* = 6) were killed immediately after completion of colonic repair. Those in group 2 (*n* = 8) and group 3 (*n* = 10) recovered from anaesthesia for 5 and 14 days respectively. During the postoperative period all animals were allowed free access to food and water.

Post-mortem assessment

The injured sections of colon were removed, their lumen lavaged and they were subjected to intraluminal distension with water up to a maximum pressure of 300 mmHg. The pressure at which any repairs failed was recorded.

Following mechanical testing, representative samples of repairs were removed and fixed in buffered neutral formaldehyde. After fixation, histological slides were prepared from wax-embedded sections, cut to a thickness of 5 µm, stained with haematoxylin and eosin, and examined using standard light microscopy. Histological evaluation was performed by a pathologist blinded to the details of the experimental groups and repair techniques.

Bacteriological methods

Samples of peritoneal fluid and faeces were submitted for both aerobic and anaerobic culture for 48 h, and isolates subsequently identified.

Statistical methods

One-way analysis of variance was used to compare the time taken for repair of colonic wounds. Results from mechanical testing were compared with survival analysis.

Results

There were two premature deaths, both occurring in animals in group 3 (14-day recovery). One occurred 2 h after the completion of surgery, and the second 4 days after operation. The presence of *Escherichia coli* in urine and blood of both animals at post mortem indicated bacteraemia as a possible cause of death, since all other blood cultures removed from all other animals were sterile.

Size of wounds

The mean dimensions of entry wounds were 7 × 6 mm, and those of the exit wounds were 5 × 5 mm.

Time for repair

The time taken to repair perforations by the two techniques is shown in *Table 1*. In all groups stapled repairs were completed significantly more quickly than sutured repairs.

Bacteriology

At the initial laparotomy all samples of peritoneal fluid were sterile. However, at the time of repair, peritoneal fluid sampled from all animals was positive for *E. coli*. In two animals there was coinfection with *Clostridium perfringens* and *Bacteroides fragilis*.

Culture of peritoneal fluid samples taken at post mortem revealed *E. coli* in all animals in group 2, and in two of the eight animals in group 3. Peritoneal fluid in the remaining six animals in group 3 was sterile.

Table 1 Time taken to complete closure of colonic perforations

	Mean(s.d.) time to complete six wound repairs (min)	
	Sutured repair	Stapled repair
Group 1	33(2·1)	5·2(1·6)*
Group 2	29(3·9)	5·5(1·8)*
Group 3	31(4·5)	3·8(1·1)*
Total for all groups	31(4·0)	4·8(1·6)*

Animals in group 1 were killed 6 h after injury, those in group 2 5 days after injury, and those in group 3 14 days after injury. *$P < 0·05$ (stapled *versus* sutured repair, analysis of variance)

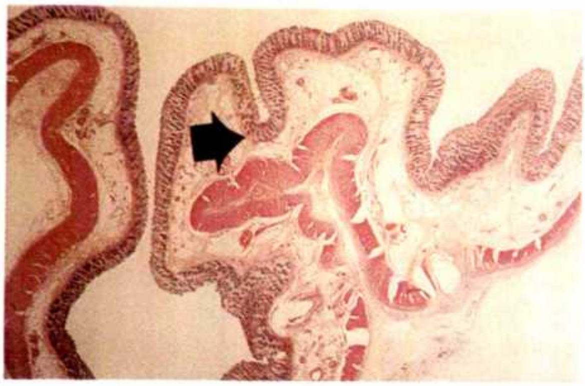

Fig. 1 Colonic perforation 14 days after repair with skin staples placed in seromuscular layers. There is continuity of the mucosa at the site of injury (➡). (Haematoxylin and eosin, 5-μm thickness; original magnification × 15)

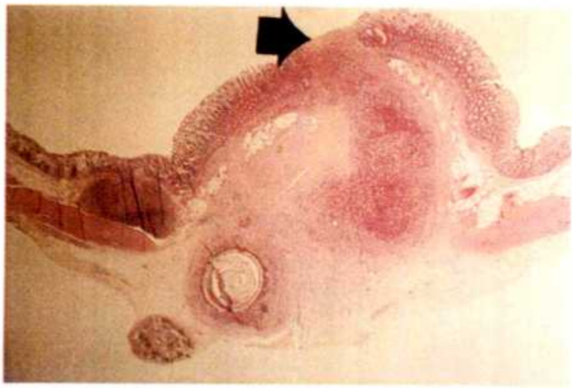

Fig. 2 Colonic perforation 14 days after repair with sutures. There is incomplete healing of the mucosa with an area of ulceration (➡). (Haematoxylin and eosin, 5-μm thickness; original magnification × 15)

Biomechanical assessment

The leak pressures for the repairs are shown in *Table 2*. There was no significant difference between the two repair techniques at any of the three time points.

Table 2 Leak pressures of colonic segments

	Mean leak pressure (mmHg)	
	Sutured repair	Stapled repair
Group 1	193 (140–282)	225 (120–300)
Group 2	221 (120–300)	247 (152–300)
Group 3	183 (120–210)	178 (135–223)

Values in parentheses are ranges, up to a maximum pressure of 300 mmHg. Animals in group 1 were killed 6 h after injury, those in group 2 5 days after injury, and those in group 3 14 days after injury

Histology

At 6 h after injury there was established peritonitis affecting both visceral and parietal peritoneum. The early histological appearances of both repair techniques were similar, although the wound edges were more closely approximated in stapled repairs. Healing was more advanced with stapled repairs by days 5 and 14. This was apparent by less mucosal ulceration at the site of repair and more complete healing of the serosa in these repairs (*Figs 1* and *2*).

Discussion

This study has demonstrated that experimental colonic perforations may be repaired rapidly and reliably using skin staples placed in the seromuscular layers, in the presence of peritonitis.

In this animal model the leakage of colonic contents into the peritoneal cavity allowed the development of a diffuse bacterial peritonitis, despite the systemic administration of antibiotics. This was confirmed by the isolation of bacteria from the peritoneal cavity in all eight animals killed at day 5 and from two of the eight killed at day 14. The persistence of bacteria in the peritoneal cavity at day 5 may be a reflection of the choice of antibiotics used, which were those specified for treating penetrating abdominal injuries in the military casualty[12]. In retrospect, the use of an antibiotic regimen based on metronidazole and a cephalosporin may have resulted in greater elimination of bacteria from the peritoneal cavity. However, the presence of bacterial peritonitis provided further evidence for the ability of the colonic wounds to heal in an adverse environment.

The interval between creating the colonic perforations and their subsequent repair aimed to model the delay between injury and definitive surgical treatment which occurs in trauma patients. Reports from civilian trauma centres, treating large numbers of patients who have sustained penetrating abdominal injury, would indicate that a delay of 6 h is unusual. In these circumstances, the time from wounding to the time of surgery is usually 90–150 min, or less[4,6]. However, in military conflicts there is often a considerable delay from wounding to surgical care, in some cases up to 12 h[3,13]. As a result these patients may be at high risk of developing complications following primary colonic repair[13].

Skin staples have been used for experimental anastomoses of small and large intestine[8,9] and for the closure of multiple intestinal perforations[11]. The present study is the first to describe the use of skin staples for colonic repair in the presence of experimental bacterial peritonitis. Despite the presence of peritonitis, skin staples were easily introduced into the seromuscular layers of the colonic wall, and repair was undertaken significantly faster compared with a technique of local excision and suture repair. An alternative technique to allow rapid closure of perforations might involve a continuous suture. However, this is not without risk of complications. Overall, the single-layer interrupted technique is probably the safest method of intestinal suture[14].

Biomechanical assessment of the integrity of colonic repair wounds may be performed with a range of techniques. Each has limitations, but intraluminal pressure testing has been shown to be a reliable and reproducible technique for normal colon[15,16]. The bursting pressures of the colonic wall in this study were supraphysiological when compared with pressures recorded from the colonic lumen *in vivo*, from humans[17]. This provided further evidence for the integrity of the repairs, despite the presence of peritonitis.

Histopathology showed differences in colonic healing according to the technique used for repair. The use of staples resulted in more complete apposition of wound edges compared with repair by sutures. By day 14 subjective evaluation of sutured wounds demonstrated more inflammation, with mucosal ulceration and evidence of giant cell reactions in the submucosa. These findings contrast with those of Dawson *et al.*[11], who described poor histological apposition of wound edges at stapled repair. However, in the latter study no attempt was made to invert the wound edges at the time of repair. Despite this there was less serosal inflammation at the site of perforations closed with staples compared with those closed by sutures[11].

The present study has demonstrated that primary repair of multiple colonic perforations may be undertaken successfully using either staples applied to the seromuscular layers of the colon, or by local excision and suture repair, in the presence of peritonitis in a pig model. These results may provide support for the consideration of the use of skin staples for the repair of damaged bowel in circumstances where there is likely to be a high throughput of acutely injured patients (e.g. surgical teams working in areas of military conflict). The technique may also be beneficial in cases where laparotomy is performed for 'damage control' in the haemodynamically unstable patient, where reducing the operating time results in improved survival in the severely injured patient[18].

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Original article

Intraoperative lymphatic mapping and sentinel lymph node biopsy for Merkel cell carcinoma

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Background: Merkel cell carcinoma is a rare cutaneous neoplasm which commonly spreads to the regional lymph nodes. The feasibility of identifying the sentinel node in patients with clinically node-negative Merkel cell carcinoma was evaluated.

Methods: Sentinel lymphatic mapping was performed in 18 patients with stage 1 Merkel cell carcinoma using the combination of isosulphan blue dye and ^{99m}Tc-radiolabelled sulphur colloid. Patients with tumour metastasis in the sentinel node underwent complete dissection of the remainder of the lymph node basin.

Results: Eighteen patients underwent removal of 35 sentinel nodes. Two patients demonstrated metastatic disease in the sentinel lymph nodes; complete dissection of the involved nodal basin revealed no additional positive nodes suggesting that the sentinel lymph node had been identified. The node-negative patients received no further surgical therapy, with no evidence of recurrent disease in the sentinel nodal basin at a median of 7 months' follow-up.

Conclusion: Sentinel node biopsy is feasible in patients with Merkel cell carcinoma. It can be used to stage patients and provides important prognostic information. In those with subclinical nodal disease, it may direct early regional lymphadenectomy but the effect of such surgery on survival remains unclear.

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Introduction

Merkel cell carcinoma is a rare cutaneous neoplasm with a distinctive trabecular architecture originally described by Toker in 1972[1]. Typically, pink or grey skin lesions present on the limbs or head and neck and, because they arise in the dermis rather than the epidermis, they rarely ulcerate[2]. The histology of Merkel cell carcinoma is now well described although its aetiology remains unknown[1,3–5]. The tumour usually affects older individuals, with a median age at presentation of 66 years[6]. Both sexes are affected, with a slight male predominance[6]. Patients with Merkel cell carcinoma are usually white although it can occur in black individuals[7].

The management of Merkel cell carcinoma remains controversial given its high propensity to metastasize to regional lymph nodes. Most surgeons have not routinely advocated elective regional lymphadenectomy in the absence of clinical evidence of nodal disease[6,8–10].

It has been shown that the histopathology of the sentinel node reflects the histology of the remaining nodes in the basin with a high degree of accuracy in both melanoma and breast cancer[11–13]. The aim of this study was to determine whether lymphatic mapping for patients with clinically node-negative Merkel cell carcinoma could be performed and to assess the safety of such a technique.

Patients and methods

One hundred and eighteen patients with Merkel cell carcinoma were treated in this centre from 1969 to 1998. Since 1996, 18 patients underwent lymphatic mapping and sentinel lymph node biopsy as part of their treatment and are the subject of this report. All patients had biopsy-proven Merkel cell carcinoma and had sentinel node biopsy performed immediately before wide local excision of the primary lesion. Patients with negative sentinel lymph nodes received no further surgical therapy to the nodal basin. Patients who were pregnant or clinically node positive were excluded from lymphatic mapping studies. Clinical variables analysed included age at diagnosis, sex, race and duration of symptoms. Pathological variables analysed included tumour site and size. Follow-up information was obtained from outpatient charts or through telephone correspondence in two patients. Systemic recurrence was excluded by physical examination alone. Adequate data and complete follow-up were available for all 18 patients.

Preoperative lymphoscintigraphy

On the morning of surgery, 0·1 mCi unfiltered ^{99m}Tc-radiolabelled sulphur colloid (CIS – US, Bedford, Massachusetts, USA) was injected at four sites intradermally around the excision biopsy scar. Lymphoscintigraphy was performed with a standard large-field-of-view γ camera immediately following injection to obtain dynamic flow and static images.

Intraoperative lymphatic mapping

The technique of intraoperative lymphatic mapping using aqueous 1 per cent lymphazurin blue (Zenith Parenterals, Rosemont, Illinois, USA) for melanoma has been described elsewhere[11,12]. In brief, at surgery before wide local excision of the primary tumour, approximately 0·8 ml blue dye was injected intradermally around the primary Merkel cell carcinoma biopsy site proximal to the tumour site, in line with the lymphatic drainage predicted by lymphoscintigraphy. After injecting the dye, the patient was prepared, draped and positioned.

An incision was made and sentinel node biopsy was performed, guided by both the γ probe (C-Trak; Care-Wise Medical, Morgan, California, USA) and the appearance of blue dye in the node(s). Complete lymph node dissection was performed under general anaesthesia only in patients with a positive sentinel node.

Histological examination of lymph nodes

Sentinel lymph nodes removed at the time of sentinel node biopsy were cut in half and subjected to frozen-section analysis initially. Specimens then underwent three serial sections and were stained conventionally with haematoxylin and eosin. Immunohistochemistry was not routinely used to examine nodes.

Results

Patient demographics are outlined in *Table 1*. All 18 patients had a previous surgical biopsy elsewhere. Preoperative lymphoscintigraphy identified the regional lymphatic drainage pattern in all 18 patients and the sentinel node was successfully identified in all 18. There were no complications related to blue dye, radiolabelled sulphur colloid or sentinel lymphadenectomy. In both of the two node-positive patients, the sentinel node was the only node involved with tumour. In one patient the frozen-section report of the sentinel node was negative and permanent deeper sections revealed malignant cells. The patient returned at a later date to have a complete axillary dissection. The mean number of sentinel nodes removed was 1·9 (range 1–6). Dual drainage to two nodal basins was not noted from any trunk lesion. At a median follow-up of 6·5 months, no patient has developed recurrence of the disease either in the nodal basin or systemically.

Table 1 Patient data

	No of patients
Sex	
M	12
F	6
Age (years)*	64 (40–80)
Caucasian	18
Site of tumour	
Head and neck	1
Buttock and trunk	6
Upper extremity	4
Lower extremity	7
Tumour size (mm)*	30 (2–100)
Duration of symptoms (months)*	6 (3–12)
Clinical stage I at presentation	18
Sentinel node histology	
Positive	2
Negative	16
Median (range) follow-up (months)	7 (1–24)

*Values are mean (range)

There were two women with positive sentinel nodes, both 80 years of age. One patient had a 50-mm lesion on the buttock for 4 months; two of 16 nodes were positive, both of which were sentinel nodes. The other patient had a 15-mm lesion on the upper arm for 3 months and had one positive sentinel node, two negative sentinel nodes and 13 other negative non-sentinel nodes.

Discussion

Merkel cell carcinoma or cutaneous neuroendocrine carcinoma is a high-grade cutaneous malignancy with a propensity for regional lymph node and distant metastasis[6,14–16]. Since its original description by Toker[1], a number of synonyms have been used to describe this neoplasm, including cutaneous APUDoma, primary small cell carcinoma of the skin, neuroendocrine carcinoma, primary undifferentiated carcinoma of the skin and endocrine carcinoma of the skin.

The sentinel node is defined as the first lymph node in a regional lymphatic basin which receives lymph flow from a primary tumour. This node is the first lymph node encountered by tumour cells spreading through lymphatic channels. The histological status of this node should therefore predict the status of the regional lymphatic basin at risk. The concept was first introduced by Cabanas for penile carcinoma in 1977[17] but was popularized in the mid-1980s by Morton and colleagues[18] for use in patients with melanoma and more recently by Giuliano *et al.*[19] for breast cancer. A consistent relationship between the histological status of the sentinel node and the presence or absence of regional disease has been demonstrated for melanoma, and selective lymphadenectomy is increasingly employed in the management of patients with this disease[20].

Melanoma and Merkel cell carcinoma have a similar natural history. As with cutaneous melanoma, the development of distant disease in patients with Merkel cell carcinoma is often preceded by regional nodal involvement[6]. In a previous review of 70 cases, regional nodal metastases occurred in 66 per cent of patients. In addition, systemic involvement was nearly uniformly preceded by the development of positive regional nodes[6].

It is controversial whether regional nodal disease is a governor of outcome, but it is certainly a predictor. Although it is reasonable to assume that sentinel node biopsy would also be useful in the selection of patients with Merkel cell carcinoma for regional lymphadenectomy, the accuracy of the technique in this group has not been established. Such a study may prove difficult to perform because of the rarity of this condition. Selective lymphadenectomy for Merkel cell carcinoma has only been reported in a total of 20 patients in three previous reports[21–23]. Although the accuracy of the technique has not been validated in patients with Merkel cell carcinoma, the present authors' early experience is encouraging.

Most surgeons do not advocate elective regional lymphadenectomy in patients with Merkel cell carcinoma[6,8–10] because this may be associated with significant morbidity, especially lymphoedema[24], shoulder dysfunction and paraesthesia. Those most likely to develop Merkel cell carcinoma are greater than 60 years of age and thus are more vulnerable to the morbidity of regional lymphadenectomy[24].

The median time for the development of clinically detectable nodal metastases in patients who present with stage 1 Merkel cell carcinoma is 7 months[6]. Median follow-up for this series is 7 months. Perhaps one could speculate that the lack of regional nodal failure in this patient population may represent the successful identification of regional node-negative patients or use of the technique in a favourable subgroup of patients with Merkel cell carcinoma.

There are advantages to using selective lymphadenectomy in the management of patients with Merkel cell carcinoma. As with melanoma, the procedure may facilitate staging of these patients. Nodal metastases are common in Merkel cell carcinoma and are a primary determinant of outcome[6,25]. Five-year survival rates for patients with nodal disease are less than 50 per cent compared with 88 per cent in the absence of regional metastases[6,14]. Tumour site, size, surgical margin, and the proximity of the lesion relative to the regional node basin have not been found to be predictive of nodal disease[6]. These characteristics support the role of tumour staging by sentinel node biopsy in order to provide prognostic information to the patient as well as to select patients for regional lymphadenectomy and possibly adjuvant therapy. Immunohistochemistry with cytokeratin and chromogranin might prove useful in further staging these patients. In patients with melanoma, a negative sentinel lymphadenectomy obviates the need for a complete lymph node dissection; only 2–4 per cent of these patients with negative sentinel nodes have developed locoregional failure[11,12,18]. Conversely, selective lymphadenectomy satisfies advocates of elective nodal dissection in that it allows resection of an early subclinical metastasis while it is still within the regional lymphatic basin, at a time when the systemic tumour burden is likely to be small.

Another benefit of selective lymphadenectomy is that it correctly identifies the lymph node basin most likely to harbour micrometastases, rather than relying on anatomical guidelines. It is well known that patients with melanoma develop lymph node metastasis in basins different from those predicted by anatomical considerations[26]. Drainage patterns identified by lymphoscintigraphy are discordant from classical teaching in 63 per cent of patients with head and neck melanoma, and 32 per cent of those with truncal melanomas[26]. Nearly 20 per cent of patients with melanoma undergo dissection of regional basins different from those that would be predicted by traditional teaching based on the results of preoperative lymphoscintigraphy[26,27]. Experience gained from patients with melanoma highlights that nodal dissections undertaken without preoperative lymphoscintigraphy are misdirected in up to 50 per cent of cases[26,27]. Mapping is ideally performed after the initial biopsy and before wide local excision, because the latter procedure could interrupt the true course of cutaneous lymphatics and result in inaccurate sentinel node localization.

The role of adjuvant therapy has not yet been established for a number of reasons. First, there are too few cases for a prospective clinical trial[28]. Second, a variety of treatment protocols have been reported with inconsistent results. Finally, there has been no clear identification of risk factors for which adjuvant therapy should be employed. Although the use of chemotherapy in the treatment of advanced irresectable disease is warranted, its role in the adjuvant setting in patients at risk for recurrence remains unproven and controversial. If chemotherapy proves to be beneficial in the adjuvant setting, then the change in the staging of Merkel cell carcinoma provided by sentinel node biopsy will be helpful.

In summary, sentinel node biopsy is feasible; it can be used to stage patients with Merkel cell carcinoma and provides important prognostic information. In those with subclinical nodal disease, it may direct early regional lymphadenectomy but the effect of such surgery on survival in Merkel cell carcinoma remains unclear.

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Comparison of radioguided excision with wire localization of occult breast lesions

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Background: Clinically occult breast lesions are found with increasing frequency as a result of the widespread use of mammographic screening.

Methods: This study reports a new localization technique in which a small quantity of ^{99m}Tc-labelled colloidal albumin is inoculated directly into the lesion under stereotactic–radiographic or ultrasonographic guidance. Correct positioning of the inoculum is checked by scintigraphy. A γ ray detection probe is then used to locate the lesion and guide its surgical removal. The results of this method in 30 patients were compared with those obtained using the established hook wire method in another 30 patients.

Results: In the wire localization group, the mean(s.d.) distance from the lesion centre to the specimen margin was 24·5(0·4) (range 15–45) mm. For the radioguided group the figures were 13·8(0·3) (range 5–25) mm. The mean(s.d.) lesion concentricity (difference between the maximum and minimum distance from the lesion border to specimen margin) was 6·2(0·4) (range 2–15) mm in the wire localization group and 3·8(0·2) (range 1–10) mm in the radioguided group.

Conclusion: Use of a γ probe allowed rapid, easy and accurate removal of occult breast lesions. In comparison to the hook wire method, radioguided removal allows reduced excision volume and better lesion centring within the specimen.

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Introduction

Until recently non-invasive tumours formed a relatively small fraction (1–5 per cent) of diagnosed breast cancers[1]. The more widespread use of mammographic screening has increased the detection of preinvasive lesions. Recent publications indicate that 15–25 per cent of breast cancers are intraductal carcinomas, most of which are clinically occult[2–9]. Precise preoperative localization of an occult breast lesion is necessary before removal, yet none of the methods currently used can be regarded as perfect[7,10–16]. A new method for localizing non-palpable breast lesions, radioguided occult lesion localization (ROLL) has been developed at the European Institute of Oncology in Milan. The present study compared ROLL with the hook wire localization technique used previously.

Materials and methods

Between March 1996 and March 1998, 331 consecutive patients underwent excision biopsy using the ROLL procedure for suspicious non-palpable breast lesions detected mammographically. Data on the first 30 patients of this series were compared with those for the last 30 patients whose lesions were localized by means of the hook wire method.

Radioguided occult lesion localization

On the day before excision, patients were injected with particles of human serum albumin 10–150 μm in diameter (Macrotec; Sorin Biomedica, Saluggia, Italy), labelled with approximately 3·7 MBq (0·1 mCi) ^{99m}Tc at a specific activity of 74 MBq/mg. The ^{99m}Tc was always freshly eluted from a generator and, after labelling, the material was assayed for free technetium according to the supplier's instructions. Assays consistently showed more than 95 per cent of the radioactive metal bound to macroaggregate.

The labelled macroaggregate (0·5 mg in 0·2 ml saline) was inoculated, without local anaesthetic, into the centre of the suspicious lesion using stereotactic mammographic guidance when only microcalcifications were present, or ultrasonographic guidance for opacities. The technique was used only when the microcalcifications were closely grouped.

In all cases, front and lateral view planar scintigraphic images of the breast (exposure time 3 min) were obtained with a γ camera (GE-Star Camm 4000; GE Medical Systems, Milwaukee, Wisconsin, USA) soon after, and 5 h after administration. Correct localization of the tracer in the lesion, and at the inoculation point only, was checked by examining these images and superimposing them (appropriately enlarged) on the mammogram (*Fig. 1*). When ultrasonography was employed to image the lesion, correct tracer localization was verified as a change in the echogenicity of the lesion site.

Excision biopsy was performed next day guided by a hand-held γ ray detection probe (C-Trak System; Care-Wise, Morgan Hill, California, USA) enclosed in a sterile glove. The γ ray detection probe is an 18 × 2-cm stainless steel tube with an angled tip for enhanced manoeuvrability. The γ rays detected by the probe are transduced into digital readout and acoustic signals. The intensity and frequency of the auditory signal are directly proportional to the level of radioactivity detected.

Using this probe the surgeon was able to find the skin projection of the lesion and decide the most appropriate incision. Having incised the skin, the area of maximum radioactivity, corresponding to the site of the lesion, was identified using the probe. The edges of the excision were defined as the locus of points surrounding the hot spot where radioactivity fell off sharply. After excising the specimen, the probe was used to check for residual radioactivity at the excision site; if this was present the excision was enlarged.

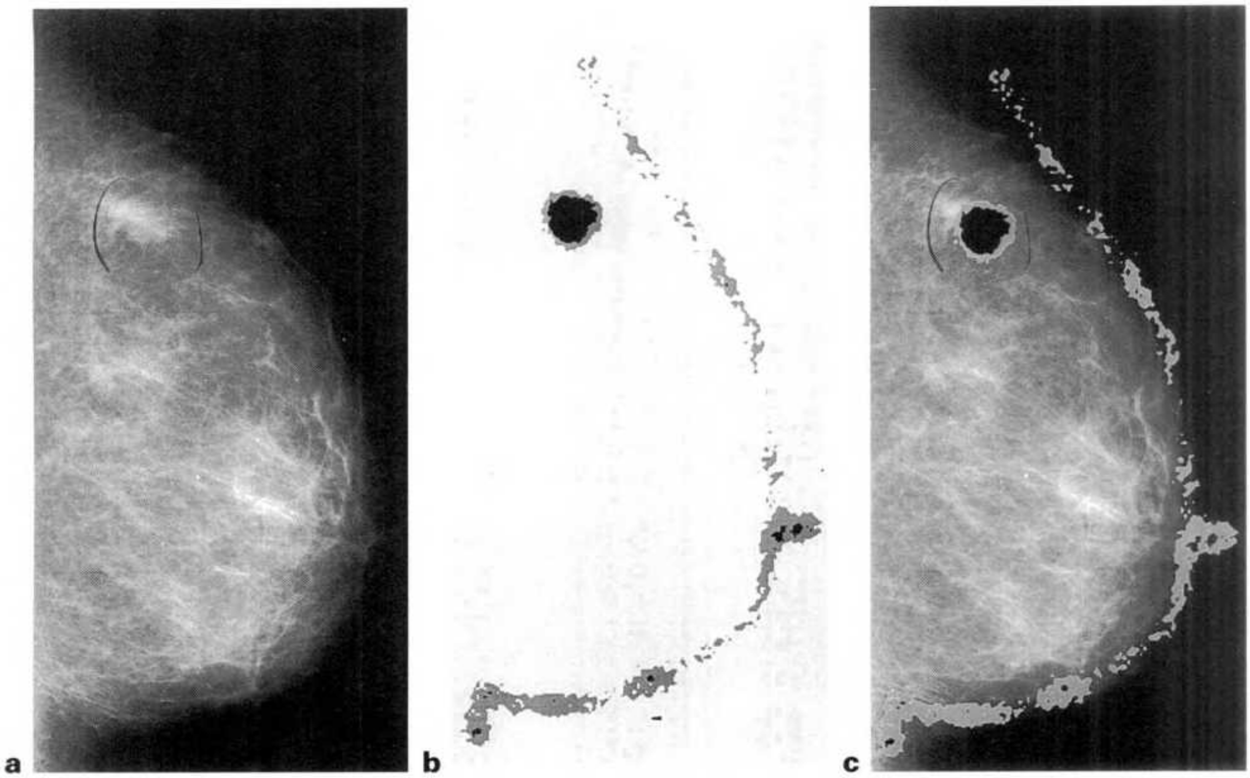

Fig. 1 **a** Mammogram showing a clinically occult lesion in the upper external quadrant of a right breast. **b** Lateral scintigraphic image of the injection position in the same patient. **c** The position of the hot spot exactly corresponds to the position of the lesion as revealed by mammography

Analysis of specimens

Surgical specimens excised using the γ ray detection probe and the guidewire were tagged with clips on one or more margins. To verify complete removal of the lesion, the specimen was placed in a special plexiglass container with the deep resection margin face down and radiographed. The concentricity of the lesion was calculated as the difference between the maximum and minimum distance from the border of the lesion to the margin of the specimen. The maximum distance from the lesion to the specimen margin was taken as an index of the quantity of tissue removed. Guidewire specimens were cut longitudinally along the wire and the distance from the margin to the needle apex was measured. The material was then sent for pathological examination.

Results

In the first 30 patients subjected to ROLL, postoperative scintigraphy of the removed specimen, as well as radiography, were used to verify the accuracy of removal. The mean distance from the centre of the lesion to the margin of the specimen was greater in the wire localization group than the ROLL group (*Table 1*). Lesions were also more concentrically placed within specimens in the ROLL group.

The pathological classification and subsequent treatments for the two groups are shown in *Table 2*. Lesions were classified according to the World Health Organization Histological Classification of Breast Tumours, as modified by Rosen and Oberman[17].

Subsequent experience

A total of 331 patients have now had lesions excised using this procedure; 225 have been described previously[18]. Inoculation of labelled albumin caused at most minimal discomfort and no adverse reactions were observed. In 328 (99·1 per cent) of 331 cases the radioactive area coincided with the lesion which was located with the probe, both on the skin projection and within breast parenchyma. In the other three patients (0·9 per cent) preoperative scintigraphy revealed a mismatch (up to 2 cm) between the radiological location of the lesion and the point of injection of the radioactivity. In both instances a wider excision surrounding the hot spot was performed; subsequent radiography of the specimen verified that the lesion had been removed completely.

Table 1 Results for the first 30 patients subjected to radioguided occult lesion localization and last 30 patients who underwent wire localization

	Distance from lesion centre to margin (mm)	Lesion concentricity (mm)*
ROLL (%)	13·8(0·3) (5–25)	3(0·2) (1–10)
Guidewire localization (%)	24·5(0·4) (15–45)	6(0·4) (2–15)

Values are mean(s.d.) (range). *Difference between the maximum and minimum distance from the border of the lesion to the margin of the specimen. ROLL, radioguided occult lesion localization

Table 2 Comparison of treatments and histology in 30 patients subjected to radioguided occult lesion localization and 30 who underwent wire localization

	ROLL (%)	Wire (%)
Malignant	59	55
Ductal carcinoma *in situ*	32	24
Infiltrating cancer	64	70
Lobular carcinoma *in situ*	5	5
Benign	41	45
Quadrantectomy alone	75	72
Quadrantectomy with axillary dissection	25	28

ROLL, radioguided occult lesion localization

Dosimetry

The mean(s.d.) absorbed dose to the inoculated area was estimated from measurements as 0·03(0·02) mGy/MBq. Because of the small quantity of material injected and the fact that it was concentrated in tissue that was removed, the absorbed dose to the breast and other tissues was negligible.

External irradiation to staff was estimated from ionization chamber (Victoreen 450P; Victoreen, Cleveland, Ohio, USA) measurements of the exposure rate in air. The mean(s.d.) air kerma rates at 0, 50 and 100 cm from the injection site immediately before surgery (around 20 h after injection) were 4·5(1·0), 1·5(0·4) and 0·9(0·3) Gy/h respectively. The mean(s.d.) absorbed dose to surgeon's hands was evaluated as 7·5(5·0) μSv/h. If 100 patients were treated per year, the absorbed dose to the surgeon's hands would correspond to 1·5(1·0) per cent and 0·2(0·1) per cent of the recommended limits for the general population (50 mSv/year) and exposed workers (500 mSv/year) respectively[19].

Discussion

Several techniques for the preoperative location of non-palpable breast lesions have been developed. The choice of technique depends on lesion characteristics, particularly site, and the equipment available[10–15]. The most frequently used method is guidewire localization (Kopans wire, Homer wire or self-retaining anchor wire) under mammographic or ultrasonographic guidance to mark the lesion site[15,16]. This has the drawback that the needle introducing the wire may be deviated or become displaced. Needle introduction is traumatic and when the wire is wrongly positioned it cannot be removed to correct its position because of the risk of bleeding and because of the difficulty in achieving more accurate positioning. If the wire becomes displaced, as often occurs when the breast is very fatty, the excised specimen may not contain all of the lesion, forcing the surgeon to perform a wider resection. In very dense breasts guidewire placement is difficult.

Radioguided excision has proved reliable and effective in localizing occult lesions[18]. After excision, the probe is used for evaluation of the lesion centricity within the specimen. Previously postoperative mammograms were used to ensure that the entire lesion was removed. Using the present method the probe is used to check that the radioactivity is contained in the centre of the specimen and that none is left at the excision site. Subsequently, radiography is used to confirm that the lesion is completely contained within the specimen.

As with all localization techniques, care is required in the initial placement of the lesion marker; in this series the radioactive tracer was positioned correctly in 99·1 per cent of patients[18]. It was then a simple matter to locate the skin projection and perform the excision, in both cases guided by the probe.

Since the radioactivity is concentrated at a point, a very small dose is required for detection. Because of the small quantity of radioactivity the dose absorbed by the patient is small. For the same reason no more than routine precautions are required by the operating team. If 100 operations were performed per year the absorbed dose to the surgeon's hands would still be less than 2 per cent of the recommended limits for the general population[19].

An advantage of the method is that the exact site of the radiolabelled lesion can be checked at any time during the operation using the probe. The surgeon can then determine the best incision to reach the lesion, independently of the site of inoculation. This results in high excision accuracy and centring of the lesion within the specimen, so that it is rarely necessary to enlarge the excision.

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Preliminary report on local resection with lymphadenectomy for early gastric cancer

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Background: The frequency of lymph node metastasis in mucosal gastric cancers 2–4 cm in diameter was low (three (1·3 per cent) of 234) in patients treated in this unit between 1966 and 1995. This study was a prospective report on local resection with lymphadenectomy for early gastric cancer.
Methods: Eight patients with a single early gastric cancer underwent local resection with lymphadenectomy. The tumour was excised with a non-cancerous rim of approximately 2 cm. The extent of lymphadenectomy depended on tumour location. Intraoperative endoscopic examination and frozen-section analysis of the dissected nodes were used to determine the resection line and evaluate nodal status.
Results: Mean operating time, blood loss and number of dissected nodes were 171 min, 87 ml and 8 respectively. There were no operative complications. Cancer invasion was confined to the mucosa in six tumours but two patients had minute submucosal invasion. The maximum diameter of the resected specimens was 10 cm and no nodal involvement was detected. No patient developed postgastrectomy syndrome.
Conclusion: For selected patients with early gastric cancer, local resection with lymphadenectomy can provide a good quality of life without compromising cure rate.

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Introduction

Local gastric resection is a standard treatment for intramural tumours such as leiomyoma and leiomyosarcoma[1] and is sometimes applied to the treatment of the other benign diseases[2,3]. This procedure has not previously been included among surgical options for gastric cancer[4]. A few reports have described local resection for gastric cancer but without lymphadenectomy[5,6]. Local resection with lymphadenectomy as treatment for early gastric cancer was developed and is currently employed at this institute. This preliminary report describes results in eight patients.

Patients and methods

Eight patients with a single gastric cancer treated between September 1996 and January 1998 were selected for local resection with lymphadenectomy. All were men, aged between 26 and 84 years. Informed consent was obtained from each patient. One patient had undergone endoscopic mucosal resection before the procedure, which was performed to remove remnant cancer.

The indication for the procedure was a mucosal gastric cancer less than 4 cm in diameter. Before operation the depth of cancer invasion was limited to the mucosa in all lesions, based on upper gastrointestinal barium studies, endoscopic examination and endoscopic ultrasonography. Lesion diameter was measured endoscopically. Patients were excluded if at operation the gastric tumour was palpable or metastatic nodes were detected by frozen-section analysis.

Surgical technique

At endoscopy before surgery, several clips were placed on the gastric mucosa approximately 2 cm outside the margin of the lesion. These sites were biopsied and confirmed to be free of cancer cells histologically.

At subsequent operation lymph node dissection was first carried out. The dissected area depended on the location of the tumour (*Fig. 1*) and was based on the lymphatic drainage of the stomach[7]. For example, when the tumour was in the lower third of the stomach along the greater curvature, the area along the right gastroepiploic vessels

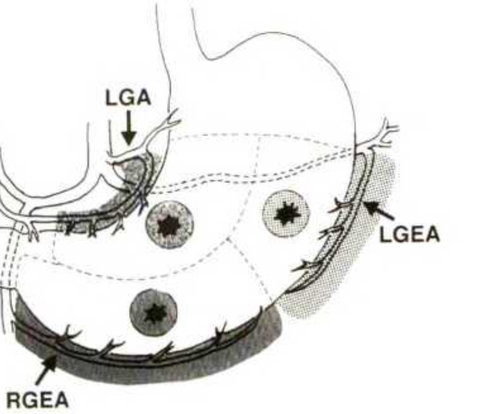

Fig. 1 Diagram of the dissected lymphatic area according to tumour location. LGA, left gastric artery; LGEA, left gastroepiploic artery; RGEA, right gastroepiploic artery

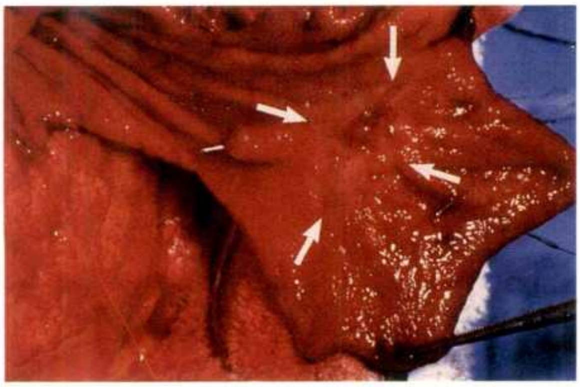

Fig. 2 Intraoperative view. Arrows indicate a depressed area involved with early gastric cancer at the centre. Two clips marking the resection margins are identified

was dissected. Several nodes among the dissected regions were submitted to frozen-section analysis during surgery. Any enlarged lymph nodes located in other sites were sampled and also submitted to frozen-section analysis.

After perigastric node dissection, intraoperative endoscopy was used to determine the resection line in the stomach. A fine needle was passed through the stomach wall from outside. Endoscopy confirmed that the needle had pierced a point outside the clips, where the absence of cancer cells had been confirmed. A traction suture was then placed at the point pierced by the needle. This procedure was repeated four times and then the marked region was excised by electrocautery. During excision, the lesion could easily be confirmed at the centre of the resection (*Fig. 2*). The gastric defect was closed with a single-layer anastomosis. During operation, the coeliac, hepatic and pyloric branches of the vagus nerve were preserved. A liquid diet was allowed on the fourth postoperative day and most patients remained in the hospital for 10–12 days. Median postoperative follow-up was 6 months.

Results

All eight selected patients underwent these procedures. The mean duration of operation was 171 (range 120–205) min and mean blood loss was 87 (30–120) ml. There were no perioperative complications. The mean number of dissected nodes was 8 (1–19). The mean diameter of the resected specimens and the tumours was 7·8 (5·9–10) cm and 2·6(1·0–4·5) cm respectively. The absence of lymph node metastasis and marginal involvement was confirmed histologically in all patients. Cancer invasion was confined to the mucosa in six tumours, but two patients had minute submucosal invasion.

All eight patients were satisfied with the surgical outcome and maintained their previous quality of life. None developed postgastrectomy symptoms. Six reported no change in food intake volume, but two noticed a slight reduction (10–20 per cent). The mean weight decreased from 64 to 61 kg during follow-up. However, the serum albumin (median 4·2 g/dl) and the total cholesterol (median 205 mg/dl) levels did not decrease in any patient.

Discussion

Before the introduction of the present procedure, gastrectomy with lymph node dissection of group 1 nodes and those along the left gastric artery was performed in this institute for mucosal cancers with a diameter of 2·0 cm or more[8]. Others employed pylorus-preserving gastrectomy with lymphadenectomy for similar lesions[9,10]. Although the frequency of nodal involvement in these cancers is low, it is not zero: lymph node metastasis was present in three (1·3 per cent) of 234 mucosal cancers with a 2–4-cm diameter in previous patients from this unit. The metastatic nodes were limited to the perigastric area. There has been no cancer recurrence in any of these 234 patients. Quality of life should be given high priority in patients with little risk of tumour recurrence. The present procedure of local resection with lymphadenectomy was developed for early gastric cancer to reduce the risk of postgastrectomy symptoms. The tumour size indication was initially set at 4 cm or less because segmental resection may be necessary for larger tumours.

Intraoperative endoscopy and frozen-section analysis of the dissected nodes were essential for determining the resection line and node status. Intraoperative diagnosis of lymph node metastasis cannot be based on macroscopic findings[11]. When nodal involvement was detected by frozen-section analysis, conventional gastrectomy with extended lymphadenectomy was indicated.

One problem with this technique is whether the gastric remnant has useful function. Gastric peristalsis should be maintained if the pacemaker zone in the proximal corpus along the greater curvature[12] is preserved. A second problem is the possibility of cancer development in the stomach remnant, although the authors' previous reports documented a low incidence after distal gastrectomy[13]. Longer follow-up is needed to clarify the frequency and significance of metachronous gastric cancer after local resection.

A third potential problem is that histological examination of the resected specimen occasionally reveals submucosal cancer invasion. The rate of lymph node metastasis from submucosal cancer with a 2–4-cm diameter was 21 (12·1 per cent) of 173 in previous patients from this institute. A palpable tumour and/or macroscopic node involvement was observed during operation in 19 of these 21 patients. In the other two, lymph node metastasis was limited to the area near the tumour. This led to the exclusion of patients with a palpable tumour or obvious nodal involvement from the present technique.

The management of patients with invasive gastric cancer remains unchanged: gastrectomy with extended lymph node dissection[8]. A small group of patients with early gastric cancer may be identified who have a good prognosis. Limited resection with lymphadenectomy may be safe in these patients, yet preserve gastric function.

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Adenocarcinomas of the distal oesophagus and gastric cardia are one clinical entity

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Background: Adenocarcinomas of the distal third of the oesophagus and the gastric cardia have similar characteristics but different staging criteria are being used. In the present study the question is addressed whether these tumours should be regarded and staged as one clinical entity.

Methods: From January 1987 to January 1997, 252 patients with an adenocarcinoma of the oesophagus ($n = 111$) or gastric cardia ($n = 141$) underwent transhiatal resection. Pathology, pathological tumour node metastasis (pTNM) stage and survival were analysed retrospectively, and a comparison was made between tumours of the oesophagus and gastric cardia.

Results: Barrett's epithelium was diagnosed in 54 per cent of oesophageal adenocarcinomas compared with 13 per cent of adenocarcinomas of the gastric cardia ($P < 0{\cdot}001$). Oesophageal carcinomas had a more favourable pT stage, fewer positive locoregional lymph nodes (pN_{1-2} 56 *versus* 62 per cent; $P = 0{\cdot}3$), but more distant metastases accounted for by positive lymph nodes around the coeliac axis (pM_1 19 *versus* 4 per cent; $P < 0{\cdot}001$). Five-year overall survival (26 *versus* 27 per cent; $P = 0{\cdot}9$) and survival according to tumour stage were no different between the groups. Multivariate analysis showed that the location of the primary tumour was not an independent prognostic factor.

Conclusion: Adenocarcinomas of the distal oesophagus and gastric cardia should be regarded as one clinical entity. Uniform staging criteria for both malignancies are recommended.

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Introduction

According to the pathological tumour node metastasis (pTNM) criteria established by the Union Internacional Contra la Cancrum (UICC) and the American Joint Committee on Cancer, carcinoma of the gastric cardia is classified as gastric cancer; carcinoma of the distal 8 cm of the oesophagus, including the intra-abdominal oesophagus, is classified as oesophageal cancer[1,2]. However, several studies suggest common risk factors and a similar phenotype for adenocarcinomas arising from the distal oesophagus and gastric cardia[3–8]. Therefore, the distinction in classification seems rather artificial.

The present study questioned whether these tumours should be regarded and staged as two separate entities. Pathology, TNM stage and survival were studied in 252 patients who underwent resection for adenocarcinoma of the distal oesophagus or gastric cardia.

Patients and methods

From 1 January 1987 to 1 January 1997, 499 patients with an adenocarcinoma of the distal oesophagus or gastric cardia were evaluated at this hospital. After preoperative analysis 391 patients were operated on with curative intent. In 59 (15 per cent) of these, resection was not possible because of metastatic spread or local irresectability. Patients who received preoperative radiation and/or chemotherapy ($n = 43$), and those who underwent oesophageal resection and total gastrectomy reconstructed by colonic interposition ($n = 25$) or a transthoracic approach with two-field lymph node dissection ($n = 12$), were excluded from the study.

The remaining 252 patients underwent transhiatal oesophageal resection and the continuity of the gastrointestinal tract was restored by a gastric tube with cervical anastomosis. In all patients a standard dissection of the perigastric, left gastric and coeliac nodes was performed. Macroscopic tumour clearance was aimed at in all cases but no extended lymph node dissection was done.

Pathology

The pathology records of all patients were reviewed. A tumour was considered to arise from the distal oesophagus when the epicentre of the mass was located in the tubular oesophagus extending from the tracheal bifurcation to the gastro-oesophageal junction including the intra-abdominal oesophagus, according to the TNM classification (International Classification of Diseases for Oncology C15·5). The tumour was considered to be cardiac when the epicentre was at the gastric cardia, defined as the area at and immediately below the gastro-oesophageal junction, extending approximately 2 cm downwards. It was preferable to rely on the muscular wall rather than on the mucosal Z-line to define the transition between oesophagus and stomach, because many tumours destroyed the cardiac mucosa. Tumours arising from the fundus or corpus of the stomach and infiltrating the gastric cardia or distal oesophagus were excluded.

Gross specimens were processed according to a standard laboratory protocol. Multiple 4-μm sections of the tumour and surrounding mucosa were taken and stained with haematoxylin and eosin. Barrett's epithelium was diagnosed when specific evidence of intestinal metaplasia was present. Lymph nodes were identified in the formalin-fixed specimens by the pathologist and subsequently evaluated for metastases.

Staging

Adenocarcinomas of the oesophagus and gastric cardia were classified according to the pTNM criteria for carcinoma of the oesophagus or stomach, established by the UICC in 1992[1].

Statistical analysis

Differences in patient and tumour characteristics and TNM classifications were assessed with the χ^2 test. Follow-up was until 1 January 1997 or until death if earlier. Overall survival rates were calculated according to the Kaplan–Meier method and included perioperative deaths. For calculation of intercurrent death-corrected survival, patients who died from causes unrelated to carcinoma were considered as withdrawn from the study at the moment of death. Differences in survival rates were assessed with the log rank test. The Cox proportional hazard model was used to evaluate various factors simultaneously. Statistical significance was set at the 5 per cent level.

Results

Some 252 patients who underwent transhiatal resection and stomach tube reconstruction for adenocarcinoma of the oesophagus or gastric cardia were included in the study. The in-hospital mortality rate was 4 per cent ($n = 9$); causes of death were anastomotic leak ($n = 3$), pneumonia and respiratory failure ($n = 3$), thrombosis of the basilar artery ($n = 1$), tracheo-oesophageal fistula ($n = 1$) and stomach tube–aortic fistula ($n = 1$).

In 111 patients the tumour originated from the distal oesophagus and in 141 patients it originated from the gastric cardia. In both groups the median age of the patients was 66 (range 33–82) years. Male : female ratios were 3·1 : 1 for patients with oesophageal tumours and 7·8 : 1 for those with gastric cardia tumours ($P = 0{\cdot}007$).

Macroscopic appearances

The median diameter of oesophageal and gastric cardia carcinomas was 4 cm. Macroscopically, 53 oesophageal adenocarcinomas (48 per cent) were limited to the distal oesophagus and 58 tumours (52 per cent) involved the cardia with a median length of 1 cm. Thirty gastric cardia tumours (21 per cent) were limited to the cardia and 111 tumours (79 per cent) showed some infiltration of the distal oesophagus (median length 1·5 cm). A mean of 13 lymph nodes was dissected out of each specimen by the pathologist (mean 3·4 nodes positive for tumour microscopically).

Microscopy

Table 1 shows the microscopic characteristics of adenocarcinomas of the oesophagus and gastric cardia. Tumour-free resection margins were achieved in 67–74 per cent of the patients. Most carcinomas were moderately (G_2) or poorly (G_3) differentiated; signet ring cells were detected in 20 per cent of the oesophageal carcinomas and 19 per cent of gastric cardia carcinomas. There was microscopic evidence of Barrett's epithelium in 54 per cent of the oesophageal carcinomas and in 13 per cent of the gastric cardia carcinomas.

Tumour stage

Gastric cardia carcinomas were more likely to be found at an advanced T stage (*Table 2*). The frequency of metastatic locoregional lymph nodes was similar in the two groups.

Table 1 Microscopic characteristics according to location of primary tumour

Microscopic characteristics	Oesophagus (n = 111)	Gastric cardia (n = 141)	*P*
Residual tumour classification			0·2
R_0 (tumour-free margins)	74 (67)	105 (74)	
R_{1-2} (tumour positive)	37 (33)	36 (26)	
Circumferential	32	30	
Distal plane of resection	1	3	
Proximal plane	3	3	
Both	1	0	
Grade of differentiation			0·6
G_1 (well)	5 (4)	5 (3)	
G_2 (moderate)	63 (57)	70 (50)	
G_3 (poor)	43 (39)	66 (47)	
Signet ring cells			0·9
Yes	22 (20)	27 (19)	
No	89 (80)	114 (81)	
Barrett's epithelium			<0·001
Yes	60 (54)	18 (13)	
No	51 (46)	123 (87)	

Values in parentheses are percentages

Table 2 Tumour node metastasis subclassification according to location of primary tumour

	Oesophagus (n = 111)	Gastric cardia (n = 141)	*P*
Tumour			0·03
T_{is}/T_1	18 (16)	9 (6)	
T_2	16 (14)	28 (20)	
T_{3-4}	77 (70)	104 (74)	
Nodes			0·3
N_0	49 (44)	53 (38)	
N_{1-2}	62 (56)	88 (62)	
Metastases			<0·001
M_0	90 (81)	136 (96)	
M_1	21 (19)	5 (4)	

Values in parentheses are percentages

Twenty-one patients (19 per cent) with adenocarcinoma of the oesophagus were classified as having metastatic disease: metastases in distant lymph nodes were detected in 19 patients, whereas two patients had visceral metastases. In 15 of 19 patients these nodes were located around the coeliac axis (N_2 for gastric carcinomas). Only three patients with gastric cardia carcinomas had positive distant nodes and two patients had visceral metastases.

Survival

Follow-up was complete for all 252 patients. Median follow-up was 19 (range 1–118) months. Median follow-up for patients who survived was 31 (range 3–118) months. The overall 3- and 5-year survival rates (n = 252) were 36 and 24 per cent respectively, with a median survival of 22 months. As only 16 patients died without suspected or proven recurrence of disease, the overall survival rate was similar to the intercurrent death-corrected 5-year survival rate (26 per cent). Therefore, only overall survival is considered further.

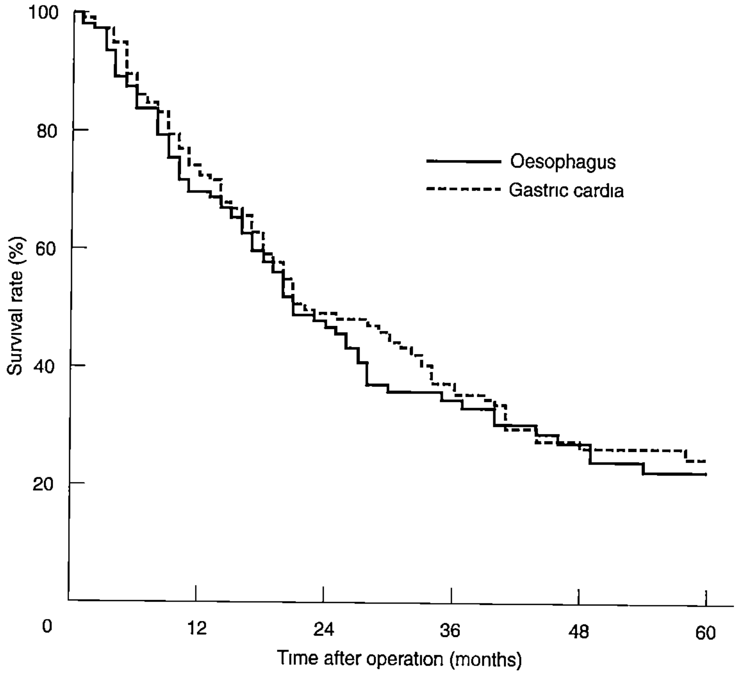
Table 3 Multivariate analysis regarding survival of various factors (Cox's regression)

Factor	No. of patients	Relative death rate	*P*
Age (years)			
< 50*	33	—	
50–60	47	1·2 (0·6–2·2)	0·6
61–70	109	1·8 (1·0–3·0)	0·03
> 71	63	2·3 (1·3–4·2)	0·004
T category			
T_{is-1}*	27	—	
T_2	44	2·1 (0·8–5·2)	0·1
T_{3-4}	181	2·4 (1·0–5·8)	0·04
N category			
N_0*	102	—	
N_{1-2}	150	2·2 (1·5–3·2)	< 0·001
M category			
M_0*	226	—	
M_1	26	1·7 (1·1–2·8)	0·03
Grade of differentiation			
G_{1-2}*	143	—	
G_3	109	1·4 (1·0–1·9)	0·05
Radicality			
R_0*	179	—	
R_{1-2}	73	1·8 (1·3–2·5)	0·01
Location of tumour			
Oesophagus*	111	—	
Gastric cardia	141	0·9 (0·7–1·3)	0·8

Values in parentheses are 95 per cent confidence intervals
*Reference categories

Survival in relation to TNM subclassifications for the whole group was as follows: patients with T_{is}/T_1 tumours had a 5-year survival rate of 70 per cent, compared with 37 per cent for T_2 and 14 per cent for those with T_{3-4} carcinomas. Patients with negative lymph nodes (N_0; n = 102) had a 5-year survival rate of 42 per cent, whereas those with positive lymph nodes (N_1 or N_2; n = 150) had a survival rate of 11 per cent ($P < 0·0001$). In the gastric cardia group the 5-year survival rate for patients with N_1 lymph nodes was not statistically different from that for patients with N_2 lymph nodes: 11 and 14 per cent respectively ($P = 0·4$). The 5-year survival rate for patients without metastasis (M_0) was 27 per cent compared with zero in patients with metastasis (M_1) ($P < 0·0001$).

Analysis for survival according to histopathological grading showed that there was a survival advantage for patients with well and moderately differentiated carcinomas (G_{1-2} 31 per cent) over patients with poorly differentiated carcinomas (G_3 18 per cent) ($P = 0·004$). The 5-year survival rate of patients with positive resection margins



No at risk	0	12	24	36	48	60
Total	252	175	100	62	42	25
Oesophagus	111	76	43	25	18	12
Gastric cardia	141	99	57	37	24	13

Fig. 1 Kaplan–Meier survival curves for patients with tumours located in the oesophagus and gastric cardia

(R$_{1-2}$) was 8 per cent and that of patients with tumour-free margins was 33 per cent ($P < 0{\cdot}0001$). When adenocarcinomas were classified as Barrett-related ($n = 78$) and non-Barrett-related ($n = 174$) carcinomas, no significant difference in survival was observed between the groups, with rates of 38 and 27 per cent respectively ($P = 0{\cdot}2$).

The 3- and 5-year survival rates for patients with oesophageal adenocarcinoma were 40 and 26 per cent respectively, and were similar to those for patients with an adenocarcinoma of the gastric cardia (38 and 27 per cent) ($P = 0{\cdot}9$; *Fig. 1*). Survival was also assessed after stratification of patients into the following groups: T_{is-2} N_0 M_0, T_{3-4} N_0 M_0, T_{is-2} N_1 M_0 and T_{3-4} N_1 M_0. No significant differences in 5-year survival rates between adenocarcinomas of the oesophagus and gastric cardia were observed within these groups.

Multivariate analysis showed that age, T, N and M category, radicality of resection and grade of differentiation were independent variables predicting survival. Location of the primary tumour was not an independent prognostic factor (*Table 3*).

Discussion

The incidence of adenocarcinomas of the oesophagus and gastric cardia has shown large increases in many populations examined[9,10]. This trend is in contrast to a decrease in the incidence of distal gastric adenocarcinomas and a relative stability of oesophageal squamous cell carcinomas. However, some studies have found only small rises in incidence or stable rates of gastric cardia cancers and non-parallel rates of oesophageal adenocarcinomas[11,12].

The present study showed that patients with gastric cardia carcinomas share characteristics in terms of age, sex distribution (predominance of men) and histological features with patients with adenocarcinomas of the distal oesophagus, as has been reported by others[6,13]. When gastric cardia carcinomas were compared with non-cardiac gastric carcinomas significant differences were found[14–16]. This suggests common risk factors and a similar phenotype for adenocarcinomas arising from the distal oesophagus and gastric cardia, and that gastric cardia tumours are more closely related to oesophageal adenocarcinomas than to distal gastric carcinomas.

It has been postulated that adenocarcinomas of the distal oesophagus arise from the Barrett metaplasia–dysplasia–carcinoma sequence, and that this might be true for all adenocarcinomas arising in the region of the lower oesophagus as well as the gastric cardia[7,17–19]. However, the risk of developing an adenocarcinoma in the intestinal metaplasia of the gastric cardia needs to be determined in larger prospective studies[20,21]. In general, the length of Barrett's epithelium in patients with an adenocarcinoma of the cardia is shorter than that in patients with oesophageal adenocarcinoma[22,23]. The low incidence of Barrett's epithelium found in the present group of cardiac carcinomas may be explained by the fact that these shorter lengths may be easily overgrown by invasive tumour[24]. These findings are identical to those of Steup *et al.*[25] but contrast with reported incidences of Barrett's metaplasia in adenocarcinomas of the gastro-oesophageal junction and gastric cardia of approximately 40 per cent[23, 26]. A possible explanation involves the difference in definition of the gastric cardia. Furthermore, the specimens were examined for the presence of Barrett's epithelium by several pathologists over the years, based on haematoxylin and eosin staining only. Interobserver variability in diagnosing Barrett's epithelium and failure to use mucin staining, which increases the sensitivity for detection of intestinal metaplasia, could be responsible for the lower prevalence of Barrett's epithelium in the present group.

A significantly better survival for patients with adenocarcinomas associated with Barrett's epithelium *versus* non-Barrett-related carcinomas has been reported[27,28]. Significant differences in survival rates were not observed in this study but a tendency towards a better survival rate was noted for the Barrett-related carcinomas. The median diameter of the tumour was 3 cm for Barrett-related carcinomas and 4·5 cm for the non-Barrett-related carcinomas. This may indicate that the so-called non-Barrett-related carcinomas are simply late tumours that have overgrown the Barrett's oesophagus and therefore show a tendency towards a worse prognosis.

Location of the tumour was not an independent prognostic parameter for survival, and 3- and 5-year overall survival rates as well as survival according to tumour stage were similar for adenocarcinomas of the oesophagus and gastric cardia. Similar results have been reported by other groups[23,25,29–31]. However, a more favourable T and N stage was seen in patients with oesophageal carcinoma. This could be explained by the fact that carcinomas of the oesophagus give rise to symptoms of dysphagia earlier and are therefore detected at an earlier stage. Moreover, the higher prevalence of early stage (T_{is}/T_1) tumours in oesophageal cancer might reflect the fact that patients with a known Barrett's oesophagus were under endoscopic surveillance at this or the referring hospital. Ruol *et al.*[32] reported prevalence rates for early cancer (T_1) of the oesophagus and cardia of 27 and 4 per cent respectively, and also found no difference in overall survival between the groups. Apparently, at the time of diagnosis cardiac tumours are at a more advanced stage of disease but this has no impact on survival.

At this institution carcinomas of the gastric cardia and the distal oesophagus are mostly treated as one clinical entity, by subtotal oesophagectomy and proximal gastrectomy. Total gastrectomy with oesophagojejunostomy for 'true' cardiac cancer not infiltrating the oesophagus, as favoured by others[33–35], is not used because of the higher risk of positive resection margins. The majority of the patients with a positive plane of resection showed involvement of the circumferential plane and only five patients (three patients with gastric cardia carcinomas) had involvement of the distal resection margin in this series. Closer analysis of the seven patients with involvement of the proximal resection plane in the neck revealed that these were all poorly differentiated carcinomas with submucosal satellite lesions infiltrating the middle and upper oesophagus.

Adenocarcinomas with their epicentre in the distal oesophagus are regarded as oesophageal carcinoma and regional lymph nodes for these carcinomas are the mediastinal and perigastric nodes, excluding the coeliac nodes. Adenocarcinomas with their epicentre at or just distal to the gastro-oesophageal junction are regarded as gastric carcinomas; regional lymph nodes are the perigastric nodes, nodes along the lesser and greater curvature (N_1 less than 3 cm and N_2 more than 3 cm from the edge of the primary tumour) and the nodes along the left gastric, common hepatic, splenic and coeliac arteries (N_2). In the individual patient assignment of the primary tumour to one of the two locations is artificial, so the analysis of lymph nodes is biased. Steup *et al.*[25] reported that, when carcinomas of the gastro-oesophageal junction were staged as oesophageal carcinomas compared with staging as gastric cancer, no major difference was seen between the two staging modalities either in overall survival or in survival by stage. Another staging system currently proposed for oesophageal carcinomas is the modified Skinner classification based on the wall node metastases (WNM) concept[36,37]. Carcinomas of the cardia are also included in this classification because the surgical approach to such lesions is similar; a comparison of staging criteria for oesophageal and gastric cancer showed no difference in the staging results[29]. In the present study 15 of 21 patients with an adenocarcinoma of the oesophagus had positive lymph nodes around the coeliac axis and were staged as M_1, whereas these would be N_2 nodes in cases of gastric cardia cancer. Therefore, these data support a classification in which involved lymph nodes resected by standard lymphadenectomy are all considered as locoregional lymph nodes for adenocarcinomas of the distal oesophagus as well the gastric cardia, and both carcinomas are regarded as one entity.

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Original article

Transhiatal approach to total gastrectomy for adenocarcinoma of the gastric cardia

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Background: A thoracoabdominal approach has traditionally been described for the resection of tumours of the gastric cardia. The aim of this study was to evaluate a transhiatal approach for resection of cancers of the gastric cardia.

Methods: Twenty consecutive patients undergoing transhiatal gastro-oesophagectomy for cancer of the gastric cardia were studied. Data were collected prospectively with regard to operating time, operative blood loss, intensive care unit (ICU) stay, analgesia use, duration of hospital stay, and pathological details of resection margin clearance and lymph node yield. Results were compared with those of the 20 preceding patients for whom the same prospective information had been recorded following resection via the standard thoracoabdominal approach.

Results: The transhiatal approach required a shorter operating time (median 190 (range 105–255) *versus* 280 (225–330) min; $P = 0{\cdot}004$). It resulted in less blood loss (median 405 (180–2000) *versus* 1000 (420–3200) ml; $P = 0{\cdot}03$) and fewer days in the ICU (median 0 (0–31) *versus* 2 (1–8) days; $P = 0{\cdot}005$) despite being performed in an older patient population (median 71 (43–78) *versus* 63 (59–70) years; $P = 0{\cdot}016$). There was no difference in either the lymph node harvest or length or involvement of upper resection margins.

Conclusion: The transhiatal approach to the resection of tumours at the gastric cardia is a valid and safe alternative to the standard thoracoabdominal technique. This technique avoids thoracotomy and its associated morbidity and is accompanied by reduced blood loss, decreased operating time and a shorter ICU stay.

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Introduction

Gastric carcinoma is the second most common cause of cancer death worldwide. While its overall incidence appears to be decreasing there has been a dramatic rise in the incidence of proximal cardia tumours at the expense of more distal tumours in the body and antrum[1]. These changes in gastric cancer subsite have focused attention on the management of cardia tumours and, in particular, the optimal surgical approach for their resection. The traditional approach to surgery with curative intent has been total gastrectomy via a thoracoabdominal approach, with extension of the abdominal incision to include a left-sided rib-fracturing thoracotomy. This approach, in an elderly population often with co-morbid cardiorespiratory disease, is associated with significant morbidity and mortality rates[2]. A modified transhiatal technique, performed under direct vision, has been described for oesophagectomy[3]. This paper describes the evaluation of a technique for radical total gastrectomy for cardia cancers which adopts this approach, thus avoiding thoracotomy.

Patients and methods

A consecutive series of 20 patients with histologically proven adenocarcinoma of the gastric cardia underwent radical resection via the transhiatal approach. Details of age, sex, operating time, operative blood loss, intensive care unit (ICU) stay, postoperative analgesic requirement and the incidence of postoperative complications were recorded. Pathological data, including tumour stage, lymph node yield and involvement or clearance of proximal resection margins, were also included. Comparison was made with the same prospectively recorded data obtained from the 20 preceding patients with adenocarcinoma of the gastric cardia who had undergone total gastrectomy via the thoracoabdominal approach. Operations were carried out between March 1991 and July 1995, and all patients were followed up for a minimum of 12 months.

Transhiatal surgical technique

A long midline incision was used, and a Goligher retractor was positioned under the xiphisternum and costal margins for cranial and lateral retraction. A standard spleen- and pancreas-preserving resection with D_2 lymphadenectomy of nodal stations 1–11 (excluding the suprapyloric and infrapyloric stations 5 and 6), in accordance with the guidelines of the Japanese Research Society for Gastric Cancer, was performed. A vertical diaphragmatic incision was made (*Fig. 1a*) two-thirds of the way along a line from the oesophageal hiatus to the xiphisternum. The incision was extended posteriorly to include the crural fibres and a cuff of diaphragm was removed in continuity with the gastrectomy specimen. This achieved not only an *en bloc* resection but also allowed good access to mediastinal lymph node groups (*Fig. 1b*). After separating the pericardium from its fat pad, the mediastinal pleura was incised and resected up to the level of the inferior pulmonary ligaments. The stomach was held forwards to allow dissection of the posterior perioesophageal tissue from the anterior surface of the aorta. The abdominal nodal dissection was extended to include the paraoesophageal and para-aortic nodal groups to the level of the inferior pulmonary ligament, with preservation of the thoracic duct. The oesophagus was transected with a macroscopically clear margin (more than 2 cm). The length of resection margin was determined by the limitations imposed by the length of jejunal loop that could be brought up from the abdomen to restore continuity. A Roux-en-Y reconstruction was then performed, with a stapled (CEEA stapler; AutoSuture, Ascot, UK) oesophagojejunal anastomosis.

Thoracoabdominal surgical technique

Patients were initially explored through an upper abdominal incision and the wound was subsequently extended to a thoracoabdominal incision along the bed of the eighth rib. A standard total gastrectomy with D_2 lymphadenectomy and splenic/pancreatic preservation as described above was carried out. The diaphragm was split in a radial fashion and, as for the transhiatal approach, the crura were excised and the mediastinal pleura resected up to the level

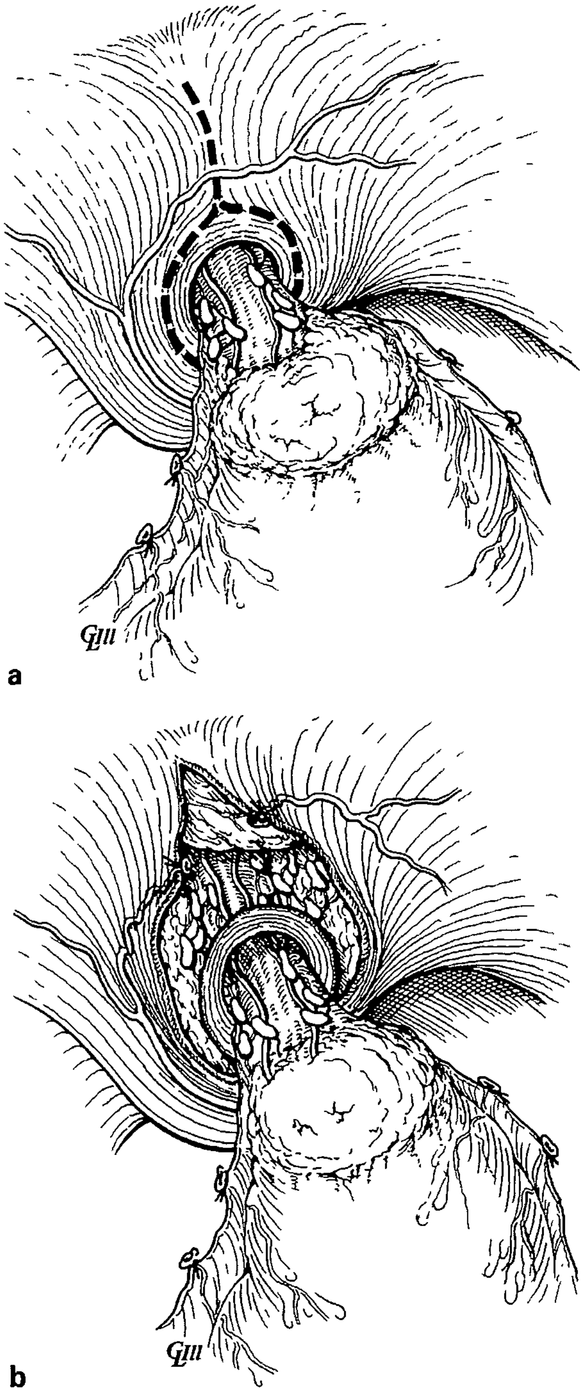

Fig. 1 a Schematic view of the undersurface of the diaphragm and proximal stomach with a tumour at the cardia. The dotted line represents the planned diaphragmatic incision. **b** After the diaphragmatic incision has been made to expose the lower oesophagus and paraoesophageal lymph node groups of the inferior pulmonary ligament. The thoracic duct was left intact and a cuff of lower oesophagus taken *en bloc* with the gastrectomy specimen. Continuity was restored with a Roux-en-Y anastomosis using a stapled (CEEA stapler) oesophagojejunal anastomosis.

Statistical analysis

Continuous data were compared with the Mann–Whitney *U* test and ordinal data by the χ^2 test.

Results

In all cases the operation was carried out by the approach planned without need for modification. There were no deaths in either series of patients. All operations were carried out by a single surgeon. Patients undergoing transhiatal resection were significantly older, with a median age of 71 (range 43–78) years compared with 63 (range 59–70) years for the thoracoabdominal group ($P = 0{\cdot}016$). The male : female ratio was 5 : 1, with no difference between patient groups. Pathological, operative and outcome data from the transhiatal and thoracoabdominal approaches are compared in *Table 1*. The two groups were similar with respect to overall disease stage as well as depth of tumour invasion and the presence of nodal metastases (T and N stages).

The median operating time for transhiatal surgery was significantly shorter at 190 (range 105–255) min compared with 280 (range 225–330) min for the thoracoabdominal approach ($P = 0{\cdot}004$). Operative blood loss ranged from 180 to 2000 (median 405) ml for the transhiatal approach and was significantly lower than that encountered with the thoracoabdominal approach (median 1000 (range 420–3200) ml). Employing the transhiatal approach resulted in a clear upper resection margin in all but four patients compared with eight in the thoracoabdominal group. The overall median clearance margin was 6 (range 0–50) mm with no significant difference for either approach. All circumferential resection margins were clear in both patient groups. Lymphadenectomy yielded a similar number of nodes for each approach (medians 23 and 19, range 8–45).

After operation all patients who had a thoracoabdominal approach were admitted to the ICU (median 2, range 1–3). Only two patients undergoing surgery via the transhaital approach required admission to ICU. For one patient this was an overnight stay and in the other admission was for 31 days. All other patients were admitted directly to the general ward. Postoperative opioid analgesia was administered through a patient-controlled analgesia system. The median requirements were 3 (range 2–8) and 4 (range 3–10) days for the transhiatal and thoracoabdominal approaches respectively.

Minor postoperative complications occurred in six patients who had transhiatal surgery and four who had thoracoabdominal surgery. Major complications occurred in three patients after transhiatal surgery: one anastomotic leak, one pulmonary embolism and one case of acute respiratory distress syndrome (ARDS). Six patients suffered major complications following thoracoabdominal surgery: two anastomotic leaks, two deep venous thromboses, one myocardial infarction and one case of ARDS

Table 1 Findings in patients who underwent resection of gastric cardia tumours by the transhiatal and thoracoabdominal approaches

	Transhiatal (*n* = 20)	Thoracoabdominal (*n* = 20)	*P*
Age (years)	71 (43–78)	63 (59–70)	0·016
Inpatient stay (days)	15 (12–87)	16 (15–63)	n.s.†
Operating time (min)	190 (105–255)	280 (225–330)	0·004
Blood loss (ml)	405 (180–2000)	1000 (420–3200)	0·034
ICU stay (days)	0 (0–31)	2 (1–8)	0·005
PCA use (days)	3 (2–8)	4 (3–10)	n.s.†
Upper resection margin (mm)	6 (0–50)	12 (0–22)	n.s.†
No. with clear upper margin*	16	12	n.s.‡
No. of lymph nodes excised	23 (10–45)	19 (8–29)	n.s.†
No. of positive lymph nodes	5 (0–25)	5 (0–24)	n.s.†
T stage	2 (1–4)	3 (1–4)	n.s.‡
N stage	2 (0–2)	2 (0–2)	n.s.‡
M stage	0 (0–1)	0 (0–1)	n.s.‡
Readmissions in 0–6 months	0 (0–2)	0	n.s.†
Readmissions in 6–12 months	0 (0–1)	0 (0–0)	n.s.†
No. with complications*	9	10	n.s.‡
No. with minor complications*	6	4	n.s.‡
No. with major complications*	3	6	n.s.‡

Values are median (range) except *no. of patients. ICU, intensive care unit; PCA, patient-controlled analgesia; n.s., not significant. †Mann–Whitney *U* test; ‡χ^2 test

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complicated by multiple organ failure. The median inpatient stay was 15 (range 12–87) days; there was no significant difference between techniques.

There were no deaths in hospital. Only two patients required readmission within the first 6 months, both of whom had undergone transhiatal surgery and one of whom was readmitted twice. Readmissions in this period were for non-specific abdominal pain in two cases and suspected, although subsequently refuted, deep venous thrombosis in another. In the second 6 months after discharge, one patient was readmitted for dilatation of a benign anastomotic stricture. No patient who had undergone thoracoabdominal surgery required readmission during this period.

Discussion

Several approaches for the resection of cancers of the gastric cardia have been described previously, including radical gastrectomy by the thoracoabdominal approach[4], proximal subtotal gastrectomy, transhiatal oesophagectomy with gastric pull through and two-stage Ivor–Lewis gastro-oesophagectomy. This is the first report of total gastrectomy for gastric cardia cancer by the transhiatal approach.

The transhiatal approach to total gastrectomy for tumours of the gastric cardia is a less time consuming procedure associated with decreased blood loss, and fewer complications compared with the traditional thoracoabdominal approach. This does not appear to be at the expense of the radicality of lymphadenectomy nor the longitudinal or circumferential margin of tumour clearance. Additionally there was a significant decrease in the need for and use of intensive care beds.

The two groups of patients were comparable in terms of overall disease stage, depth of tumour invasion and American Society of Anesthesiologists grade. However, patients undergoing dissection through the transhiatal approach were significantly older. In spite of this, a lower perioperative morbidity rate and reduced patient dependency in the immediate postoperative period were achieved with the transhiatal approach. The reduced reliance on ICU beds has important cost implications and benefits. The more widespread use of a high-dependency unit for the care of such patients in the immediate postoperative period may decrease this benefit.

The arguments for and against the transhiatal approach are well documented for the treatment of oesophageal cancer[5–9]. Skinner and colleagues[10] have argued in favour of thoracotomy for distal oesophageal tumours in order to allow radical *en bloc* dissection to be performed. Several reports have suggested that surgery involving thoracotomy is associated with considerable respiratory complications[8] and wound pain[11]. This has led many surgeons to favour the transhiatal approach for lower oesophageal cancer resection on the grounds that the survival benefit from extended lymphadenectomy in advanced disease (the majority of cases) is outweighed by the added morbidity associated with thoracotomy[12]. This argument is not, however, relevant for cardia tumours as the role of lymphadenectomy for gastric cancer is better established in terms of its impact on survival and cure.

In the procedure described, lymphadenectomy is as extensive as that achievable via a thoracoabdominal approach. The pattern of lymph node dissemination is well documented in cases of distal gastric cancer and squamous cell carcinoma of the oesophagus, but is not as clear for adenocarcinomas of the oesophagogastric junction. For cardia tumours encroaching upon the junction there may be a role for more extensive mediastinal lymphadenectomy, particularly of the para-aortic and perioesophageal nodes. Access to these stations via the transhiatal approach is as good if not better than that for the thoracoabdominal approach as the height of dissection achievable in the posterior mediastinum is similar for both approaches.

The relatively high incidence of positive resection margins is a cause for concern. The need for a tumour-free surgical margin should be considered in the context of tumour node metastasis staging; several studies have demonstrated that patients with positive margins undergoing palliative resection died from other manifestations before clinical evidence of locoregional recurrence[13,14]. Use of other modalities for the assessment of tumour margins, such as endoluminal ultrasonography, or the more widespread use of intraoperative frozen-section analysis may reduce the rate of positive resection margins. However, if total gastrectomy with Roux-en-Y reconstruction is to be performed for cardia cancers, positive resection margins may be unavoidable. The extent of proximal tumour clearance in this situation is not limited by surgical access but by the length of jejunal loop which can be raised.

Transhiatal oesophagectomy and partial gastrectomy with gastric remnant pull through is an alternative favoured by some as it potentially allows greater proximal clearance. However, this technique is most often used for low oesophageal tumours; for oncological reasons the perigastric lymphadenectomy required for cardia tumours is more extensive and may lead to compromise of the vasculature of the gastric tube brought up for oesophageal reconstruction. Thoracotomy with colonic interposition may overcome this problem, although the higher morbidity and mortality rates associated with the procedure probably confine its suitability to a small group of young patients with early tumours[15]. Other techniques such as proximal gastrectomy alone have fallen from favour as patients are prone to suffer from profound bile and acid reflux, and this configuration often results in a poor functional outcome[16].

These results suggest that total radical gastrectomy via the transhiatal approach for patients with tumours at the gastric cardia is a relatively short operation associated with few postoperative complications and low levels of postoperative dependency. Further prospective studies are needed to confirm the adequacy of long-term locoregional control by this procedure, although preliminary results (up to 1 year) are as good as those achievable with the thoracoabdominal approach.

Acknowledgements

Figures 1a and *b* were drawn by Gillian Lee Illustrations.

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Indication for and outcome of laparoscopy-assisted Billroth I gastrectomy

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Background: Since 1991, laparoscopy-assisted Billroth I gastrectomy has been used for patients with early gastric cancer. The aim of this study was to clarify the outcome of 40 patients who underwent this operation and to examine the indications based on a retrospective histological study of 248 resected cases of early gastric cancer.

Methods: Operating time, blood loss, length of skin incision, and postoperative hospital stay and complications were examined using the operation records and medical charts. The presence or absence of lymph node metastasis, tumour size, site, gross type, histological type, depth of invasion, presence or absence of ulceration, and status of lymph node metastasis were investigated in 248 early gastric cancers.

Results: The mean operating time was 3 h and 48 min and the mean length of skin incision was 5·8 cm. Although one patient who had suffered from chronic bronchitis developed pneumonia and wound dehiscence, no other patients had a postoperative complication. The mean hospital stay after operation was 16 days and all patients were alive without recurrence at a median follow-up of 21 months. The incidence of lymph node metastasis in early gastric cancer was 2 per cent (three of 130) in mucosal cancers and 14 per cent (17 of 118) in submucosal cancers. These lesions could have been completely resected by laparoscopy-assisted gastrectomy.

Conclusion: All 40 patients were treated successfully by laparoscopy-assisted Billroth I gastrectomy without significant complications and with no recurrences to date. Pathological study of conventionally resected stomach and lymph nodes confirmed that laparoscopy-assisted Billroth I gastrectomy would be a safe and useful operation for most early gastric cancers.

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Introduction

With rapid advances and the wide range of instruments for laparoscopic surgery, current indications for laparoscopic gastric surgery include benign and malignant diseases[1–5]. Among gastric malignancies, early gastric cancers that are confined within the mucosa or submucosa are candidates for laparoscopic gastrectomy, since lymph node metastasis is rare and, if present, is restricted to the perigastric lymph nodes.

In 1991, the authors first performed a simple technique of laparoscopy-assisted Billroth I gastrectomy for mucosal cancer of the stomach[6]. In 1995, Watson *et al.*[7] reported a patient who underwent laparoscopic Billroth II gastrectomy for node-negative early gastric cancer. Recently, Goh *et al.*[8] reviewed questionnaires obtained from 16 surgeons around the world; laparoscopic gastrectomy was considered to be superior to conventional open gastrectomy by ten surgeons because of faster recovery, less pain and better cosmesis.

Since 1994, laparoscopy-assisted Billroth I gastrectomy for early gastric cancer has been done in this hospital. Compared with open gastrectomy, the procedure is associated with less pain, faster recovery, shorter hospital stay and a better quality of life after operation. Because the resected stomach must be extracted through a minilaparotomy wound, totally laparoscopic gastrectomy for gastric cancer is thought to be hazardous. This study clarified the outcome of 40 patients who underwent laparoscopy-assisted Billroth I gastrectomy and examined the indications for this operation based on retrospective histological study of 248 resected cases of early gastric cancer.

Patients and methods

Billroth I gastrectomy

From November 1994 to August 1997, 40 patients with early gastric cancer that was diagnosed before operation as a tumour invading the mucosa or superficial submucosa were treated by laparoscopy-assisted Billroth I gastrectomy. The indication for this procedure was determined by the depth of invasion assessed by barium meal study, endoscopy and endoscopic ultrasonography. The accuracy of preoperative diagnosis for mucosal cancer was over 90 per cent. The laparoscopy-assisted surgery was performed mainly by one skilled surgeon (S. K.). Operating time, blood loss, length of skin incision, postoperative hospital stay and complications, and pathology of the resected stomach and dissected lymph nodes were examined using the operation records, medical charts and pathology reports.

Under general anaesthesia with tracheal intubation, pneumoperitoneum of 10 mmHg was created and a laparoscope was inserted through the subumbilical incision. Four cannulas for grasping and dissecting instruments were placed in the upper abdomen. The greater omentum and gastrocolic ligament were divided by a newly designed single dissector (GCP-1; Kishiya, Fukuoka, Japan)[9] with intermittent coagulation. This dissector was useful for one-hand operation involving three fundamental functions: grasping, cutting and parting the tissues. The right gastroepiploic artery was cut between clips and ligatures. The lesser omentum was opened and the right gastric artery was divided between clips. The stomach was fully mobilized, and the left gastric artery and vein were divided using clips and ligatures. A 5-cm long upper midline skin incision was made and the mobilized stomach was pulled out through this minilaparotomy wound. The distal two-thirds of the stomach was resected using staplers (Proximate Linear Cutter; Ethicon, Ohio, USA). Complete removal of perigastric nodes and those along the left gastric artery (no. 7) was performed. Billroth I gastroduodenostomy was carried out through a minilaparotomy wound, with the same handsewn technique as used for conventional open surgery. Irrigation and observation of the abdominal cavity was achieved under pneumoperitoneum created by a new sealing device (Sandwich-disc; Takasago Medical Industry, Tokyo, Japan)[10]. Finally, the 5-cm skin incision was closed in layers.

Histological study

From October 1982 to March 1997, 248 patients underwent curative gastrectomy for early gastric cancer in this department. The presence or absence of lymph node metastasis was examined and, if present, the tumour size, site, gross type, histological type, depth of invasion, presence or absence of ulceration, and status of lymph node metastasis were investigated.

Results

Outcome of laparoscopy-assisted Billroth I gastrectomy

Table 1 shows data for 40 patients who underwent laparoscopy-assisted Billroth I gastrectomy. One patient, who had suffered from chronic bronchitis developed pneumonia and wound dehiscence. There were no other complications.

Table 2 shows the pathological findings of the resected cancers. Lymph node metastasis was not recognized in 27 tumours confined to the mucosa, but was present in three of 13 tumours invading the submucosa. In these three, metastasis was restricted to the perigastric lymph nodes (n1); one patient had three positive nodes and two had one

Table 1 Data for 40 patients who had laparoscopy-assisted Billroth I gastrectomy

Age (years)*	66 (45–82)
Sex ratio (M : F)	22 : 18
Operating time (min)*	228 (150–390)
Blood loss (ml)*	119 (10–475)
Skin incision (cm)*	5·8 (4·0–8·0)
Postoperative hospital stay (days)*	16 (12–55)

*Values are mean (range)

Table 2 Pathological findings of the cancers resected by laparoscopic-assisted procedure

	No. of tumours
Site	
Antrum	13
Body	27
Size (cm)*	2·5 (0·2–6·5)
Gross type	
Depressed (IIc)	29
Elevated (IIa)	7
Mixed (IIa + IIc)	4
Histological type	
Well differentiated	32
Poorly differentiated	8
Depth of invasion	
Mucosa	27
Submucosa	13
Lymph node metastasis	
Negative	37
Positive	3

*Values are mean (range)

positive node. In these patients, additional lymphadenectomy was not performed.

Follow-up ranged from 10 to 45 (median 21) months. All patients were alive without recurrence or port-site metastasis.

Pathological features of early gastric cancer

Three of 130 cancers confined within the mucosa (2 per cent) and 17 of 118 cancers invading the submucosa (14 per cent) had lymph node metastasis. There were 16 patients with perigastric lymph node metastases and four with level 2 node metastasis (node groups 7 and 8). Although tumour size more than 5 cm, deep submucosal invasion and histologically well differentiated type were associated with level 2 lymph node metastasis (no. 7 and 8), all mucosal cancers and most submucosal cancers could have been resected completely by laparoscopy-assisted Billroth I gastrectomy.

Discussion

The prognosis for patients with early gastric cancer or node-negative gastric cancer is excellent, and the 10-year survival rate after D_2 or D_3 gastrectomy is over 90 per cent[11,12]. Iriyama *et al.*[13] advocate that extensive lymphadenectomy is not mandatory for patients with intramucosal gastric cancer of the grossly elevated type. Sano *et al.*[14] indicate that lymph node metastasis from early gastric cancer is rare when the lesion is (1) confined to the mucosa, (2) less than 1·5 cm in diameter, (3) macroscopically elevated, (4) macroscopically depressed (IIc) without ulceration and (5) histologically well differentiated. When the lesion satisfies these criteria, less invasive surgery or endoscopic resection can be justified[1,13–16]. After endoscopic resection, however, residual cancer cells are sometimes recognized and positive perigastric lymph nodes are occasionally left behind[17]. Endoscopic resection must be applied to early gastric cancers under strict criteria, and surgical gastrectomy may be the treatment of choice when there is submucosal invasion.

In this department, endoscopic resection for early gastric cancer is indicated when the lesion is a mucosal cancer of the elevated type measuring less than 2 cm in size, or when the lesion is a mucosal cancer of the depressed type measuring less than 1 cm in size without ulceration. Poorly differentiated tumours must be excluded from indications for endoscopic mucosal resection and laparoscopic wedge resection. However, laparoscopy-assisted gastrectomy can be performed irrespective of the histological type of the tumour. Therefore, laparoscopy-assisted Billroth I gastrectomy has been indicated for early gastric cancers which are not candidates for endoscopic resection or those in which residual cancer is suspected to remain after endoscopic resection. In this study all 40 patients were treated successfully by this technique without significant complications and with no recurrences. Pathological examination of the resected stomach and lymph nodes confirmed that the malignant tissue was resected completely and that lymph node dissection was sufficient.

The present retrospective histological study of early gastric cancers demonstrated that all gastric cancers restricted to the mucosa were thought to be completely treated by D_1 gastrectomy. Although lymph node metastasis was present in 17 of 118 cancers invading the submucosa, it was restricted to the perigastric lymph nodes in 13, and to the lymph nodes around the gastric wall and along the left gastric artery (no. 7) in three. Since resection of the distal two-thirds of the stomach and Billroth I gastroduodenostomy is achieved through a minilaparotomy wound, with the same technique and instruments as used for the conventional open surgery, complete removal of the lymph nodes along the left gastric artery and additional lymph node dissection along the common hepatic artery can be done in this laparoscopy-assisted gastrectomy.

Adachi *et al.*[18] have shown that tumour size serves as a simple predictor of tumour progression, and that tumours less than 4 cm in size are mostly node negative and seldom have level 2 lymph node metastasis. Laparoscopy-assisted Billroth I gastrectomy could therefore be used for patients with tumours less than 4 cm in size. Cancers invading the mucosa, submucosa or muscularis propria without lymph node metastasis are also suitable for laparoscopy-assisted gastrectomy, since the surgical results for such tumours are better than those for node-positive early gastric cancers[19].

Recently, Adachi *et al.*[20] demonstrated that quality of life is better after laparoscopy-assisted Billroth I gastrectomy than after conventional open gastrectomy. In this study, the mean hospital stay after laparoscopy-assisted gastrectomy (16 days) was also shorter than that after open gastrectomy (22 days). These results may be due to less pain and faster recovery after laparoscopy-assisted gastrectomy. It is possible that, when laparoscopy-assisted gastrectomy is performed in Western countries, hospital stay after operation will be much shorter.

The authors believe that laparoscopy-assisted Billroth I gastrectomy is a safe and useful operation for most early gastric cancers. To confirm the feasibility and usefulness of this technique, a randomized controlled trial comparing laparoscopy-assisted gastrectomy with conventional open gastrectomy is now under way.

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Gastrointestinal stromal sarcomas

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Background: Gastrointestinal stromal sarcomas are a rare group of malignancies originating in the bowel wall.

Methods: The treatment of 12 patients with gastrointestinal stromal sarcoma who underwent operation between 1994 and 1998 was reviewed.

Results: Eight tumours originated in the stomach; others were in the small bowel or rectum. Five of the tumours were of myogenic origin, two were gastrointestinal autonomic nerve tumours, one was a mixed neural–myoid tumour, and four could not be differentiated. Complete resection was possible in ten patients; in two of the ten *en bloc* resection of adjacent organs was required to ensure adequate margins. The tumours in the remaining two patients were irresectable because of diffuse intra-abdominal metastatic disease. All patients who underwent complete resection were alive after 4–48 (median 14) months. Two of the ten patients developed recurrence, which was reresected completely. The patients with metastatic disease died less than 1 year after operation.

Conclusion: Aggressive surgical resection, achieving complete resection, can lead to prolongation of life and may be a potential cure for patients with gastrointestinal stromal sarcoma.

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Introduction

Gastrointestinal stromal sarcoma (GISS) is a rare malignant tumour of the alimentary tract. It forms part of a larger group of tumours named gastrointestinal stromal tumours (GISTs)[1]. GISTs are mesenchymal neoplasms originating in the muscular wall of hollow viscera. They are relatively rare compared with gastrointestinal neoplasms arising from the epithelium. Given their location in the muscular wall, the frequent fascicular spindle-cell growth pattern and the occurrence of similar lesions in the uterus, they were first thought to be smooth muscle proliferations with an unusual histological appearance. However, over the years ultrastructural and immunohistochemical studies have demonstrated that some of these tumours can exhibit neural ganglionic (enteric plexus) and even mixed neural–myoid histological features[2,3]. Based on the studies available to date, it would seem reasonable to speculate that such tumours may be derived from pluripotential mesenchymal cells of the gastrointestinal tract bearing the capability for either partial, incomplete or terminal differentiation along the variety of cell lines, including neural, ganglionic and myogenic.

The nomenclature of these tumours has undergone numerous changes over the years, mirroring the controversy surrounding their histogenesis. Based on recent information, GISTs are divided into three groups[2]: (1) those showing well defined or fully realized lines of differentiation such as leiomyomas and schwannomas; (2) those with either poorly differentiated features or only partial or incomplete features of differentiation but with no histological signs of malignancy, or borderline or undetermined characteristics; and (3) those showing malignant characteristics which are defined as GISS.

Most descriptions of GISS have come from pathologists concentrating on the histopathological and immunohistochemical features, and less on biological behaviour, treatment and prognosis. The authors present their experience of treating patients with such neoplasms.

Patients and methods

Twelve patients with GISS were operated on in the authors' surgical department between 1994 and 1998. Charts and histopathological slides were reviewed to determine clinical presentation, histological type and malignant features, extent of surgical resection, operative morbidity and mortality, the use of radiation and/or chemotherapy, pattern of recurrence and metastasis, and survival.

Histological subtype was determined by haematoxylin and eosin-stained specimens visualized via light microscopy, immunohistochemical reactions with vimentin, actin, desmin, synaptophysin, chromogranin, neurone-specific enolase, neurofilaments, LE47, S-100 protein, Bcl-2 and CD34, and by electron microscopy. All tumours had two or more morphological criteria for malignancy[2]: size greater than 5 cm in diameter, infiltration of adjacent organs, presence of tumour necrosis, mitotic count greater than 1 per 10 high-power fields, and infiltration of the mucosa overlying the lesion. Although none of these features by themselves constitutes definitive evidence of malignancy, the presence of two or more within a single lesion is highly suggestive of a malignant process and warrants designation of the tumour as a sarcoma.

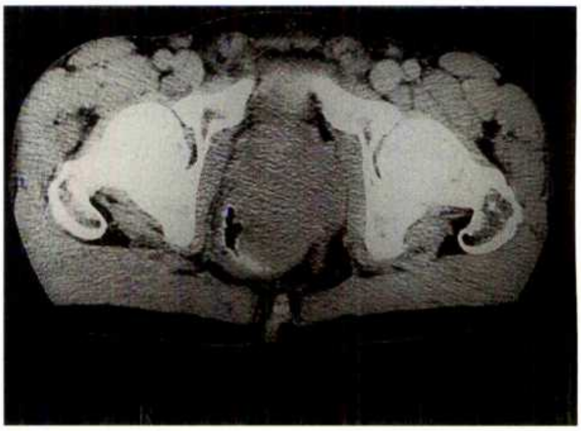

Fig. 1 Computed tomogram of a 44-year-old patient with a mixed neural–myoid type of gastrointestinal stromal sarcoma originating in the rectum. A 12-cm mass filling the rectal lumen and pushing aside the pelvic viscera is demonstrated

Results

There were seven women and five men, aged 27–80 (mean 56) years. The most common presenting complaint was abdominal pain (four patients). Three patients had evidence of gastrointestinal blood loss. One patient had anorexia, nausea, vomiting and weight loss. Another had complete small bowel obstruction as the presenting symptom. Three patients were asymptomatic and were diagnosed incidentally through imaging studies performed for some other reason or at laparotomy. An abdominal mass was palpable on physical examination in four patients.

The preoperative assessment included ultrasonography, computed tomography (*Fig. 1*) or magnetic resonance imaging, and endoscopic examination as needed. Eight tumours were located in the stomach (*Table 1*); others were in the small bowel or rectum. None of the tumours had metastasized to the lymph nodes. One patient had multifocal disease in the stomach and jejunum. Mean tumour diameter was 8·3 (range 5–17) cm.

All patients underwent operation. Two patients did not undergo resection because of diffuse metastatic disease which had not been demonstrated by preoperative radiological tests; one had a biopsy alone and the other underwent gastrojejunostomy for gastric outlet obstruction. Ten patients underwent complete resection. In two of these ten patients, complete resection necessitated resection of adjacent organs to ensure adequate margins. Two patients had wound infections. No other major complications were observed. There was no perioperative death. The patients with metastatic disease received doxorubicin-based chemotherapy after operation.

On histological examination five tumours were of myogenic origin (*Table 1*), two were gastrointestinal

Table 1 Tumour characteristics

Patient no.	Location	Size (cm)	Histological subtype	Mitosis*	Necrosis	Invasion to mucosa	Invasion to adjacent organs
1	Stomach and jejunum	8 and 4·5	GANT	12	+	+	–
2	Stomach	MMLs	Myogenic	5	–	+	+
3	Stomach	8	Myogenic	2	+	–	–
4	Stomach	MMLs	Myogenic	18	+	+	+
5	Stomach	10	Undifferentiated	17	+	+	+
6	Rectum	5	GANT	2	+	–	–
7	Jejunum	17	Undifferentiated	3	–	+	+
8	Stomach	5	Undifferentiated	8	–	–	–
9	Stomach	8	Undifferentiated	2	–	–	–
10	Rectum	12	Mixed neural–myoid	3	+	+	–
11	Small bowel	8	Myogenic	7	+	–	–
12	Stomach	6	Myogenic	3	+	–	–

*Number of mitoses per 10 high-power fields. GANT, gastrointestinal autonomic nerve tumour; MMLs, multiple metastatic lesions

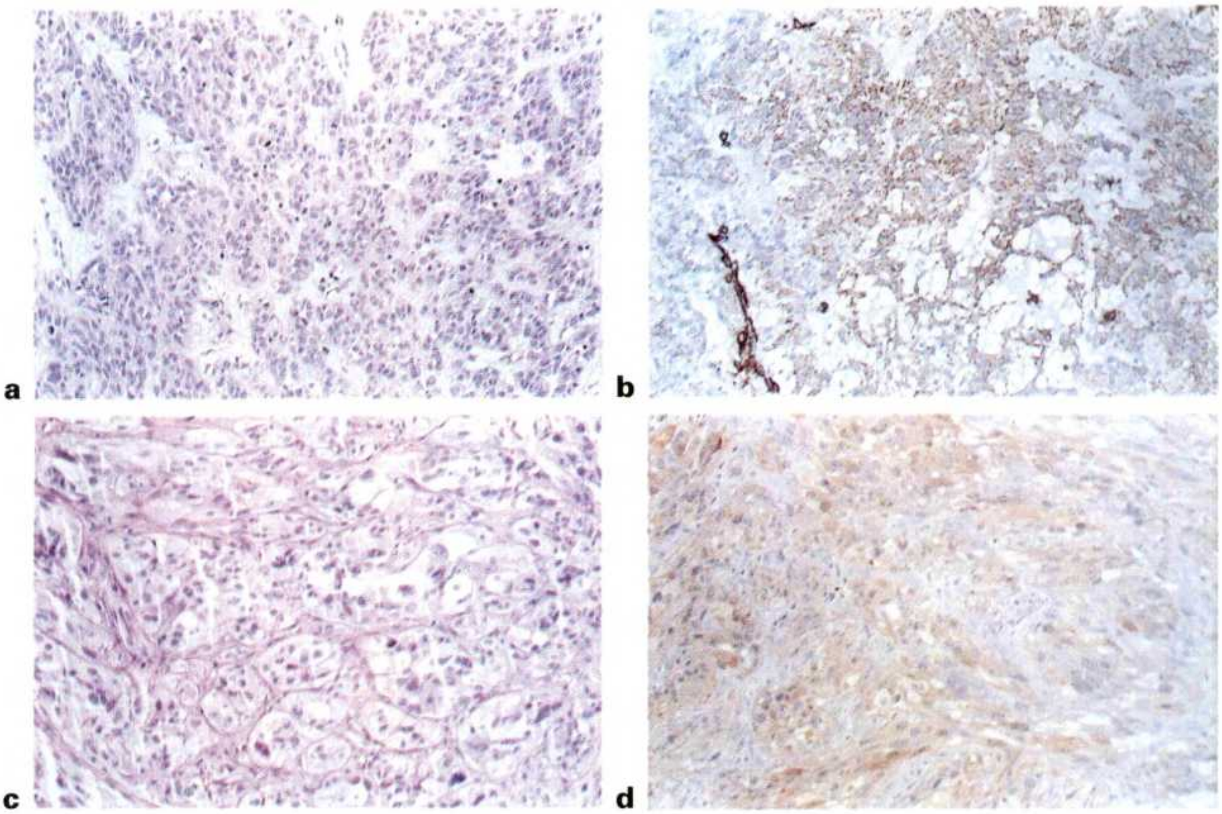

Fig. 2 **a** Gastrointestinal stromal sarcoma (GISS) with primitive myoid differentiation (haematoxylin and eosin stain, original magnification × 100). **b** Immunostaining shows the tumour cells to be positive for smooth muscle actin (original magnification × 100). **c** GISS with primitive autonomic nerve and ganglionic differentiation (haematoxylin and eosin stain, original magnification × 200). **d** Positivity for S-100 immunostain (original magnification × 200)

autonomic nerve tumours originating in the autonomic nerve plexus of the bowel wall, and one was a mixed neural–myoid tumour (*Fig. 2*). The remaining four tumours could not be differentiated. All tumours had two or more malignant characteristics. Five patients had a high-grade malignancy (more than 5 mitoses per 10 high-power fields). No difference in the grade of malignancy could be seen among the different histological subtypes.

Adjuvant therapy (chemotherapy with or without radiotherapy) was given to two patients who underwent complete resection but whose tumours were considered to have a more aggressive character because of their large size and histological appearance.

Follow-up

All patients who underwent complete resection were alive 4–48 (median 14) months after operation. Two of these patients had recurrent disease at 12 and 28 months, necessitating a second operation. The recurrence, although local, invaded adjacent organs (the spleen and pancreas in one patient, the liver and mesocolon in the other), but in both cases was amenable to complete resection. One of these patients also received adjuvant chemotherapy. Both patients were alive, 33 and 7 months after the second operation.

The remaining eight patients were alive with no evidence of disease. The two patients diagnosed with metastatic disease died 7 and 12 months after operation.

Discussion

GISSs are uncommon malignant tumours which represent 2–5% of all soft tissue sarcomas[4]. They can occur throughout the alimentary tract but, as demonstrated in this series, they are most commonly found in the stomach, affecting oesophagus (5 per cent), stomach (47 per cent), small bowel (35 per cent) and colorectum (12 per cent)[5].

Common presentations include abdominal pain, gastrointestinal bleeding, a palpable mass, and symptoms of intestinal obstruction[4]. Of note is that, unlike retroperitoneal soft tissue sarcomas, more than two-thirds of patients with GISS are symptomatic at an early stage owing to the location of the tumour in the gastrointestinal tract, while the mean tumour diameter is relatively small (8·3 cm in this series), and tumours are thus more amenable to early treatment and complete resection. Retroperitoneal sarcoma, by comparison, rarely causes symptoms until a mass is palpable when tumour diameter is 15–20 cm[6].

In this study, endoscopic ultrasonography was used during gastroscopy or transrectally in five patients with an excellent view of the size, extent and relationship of the tumour to adjacent viscera. With fibreoptic endoscopy, a tissue diagnosis may also be made which could aid in pretreatment management decisions. Deep biopsies should be performed in order to acquire an adequate tumour sample.

Some authors advocate percutaneous guided biopsy. Although fine-needle aspiration can be used to diagnose the presence of sarcoma reliably, it does not generate adequate tissue for grading. Core-needle biopsy is associated with a danger of transperitoneal or needle route dissemination of cancer cells. All patients in the present series were operated on without such a biopsy.

Based on ultrastructural examination and immunohistochemical analysis, GISSs are classified as either myogenic or neural in origin. In comparison to retroperitoneal soft tissue sarcomas, which are mainly of a high grade, GISSs are less biologically aggressive in terms of tumour grade[6].

Surgical resection is the treatment of choice for GISS[7,8]. All tumours should be approached with the intention of performing complete *en bloc* resection of the tumour and surrounding normal tissue. GISSs are limited by the organ's serosa and have no 'reactive zone'. Therefore, extended resection provides no survival benefit over wide local excision. Several reviews have shown that small tumours (5 cm or less) of the stomach can be treated adequately by wedge gastric resection with a generous margin of normal gastric wall[9]. Larger gastric sarcomas may require subtotal or total gastrectomy, including omentectomy, and some surgeons even suggest resection of juxtagastric lymph nodes. There is a discrepancy in the literature regarding the prevalence of nodal spread of gastrointestinal sarcomas[10,11]. In the present study, no patient had lymph node involvement and therefore the authors do not recommend extensive lymph node dissection during curative resection for GISS. Two of ten patients required resection of more than one intra-abdominal organ, enabling complete resection in all cases where this was attempted.

Reported survival data after surgery for GISS vary widely[5,7–12]. The rates for curative resection of gastric sarcoma range from 68 to 90 per cent, with an overall 5-year survival rate of between 19 and 56 per cent, and a 5-year survival rate following curative resection of 32–63 per cent. Reports on sarcoma of the small and large intestine have been more consistent with 5-year survival rates of between 40 and 50 per cent for all patients following complete excision[5,11,12]. None of the present patients who underwent complete resection died, whereas the two with metastatic disease had a very dismal prognosis and died less than 1 year after operation.

The role of chemotherapy and/or radiotherapy has yet to be determined. There are no data to support the administration of adjuvant chemotherapy or radiotherapy following complete surgical removal of GISS. Two patients in the present series were treated with such a regimen. However, given the available data and considering the relatively good prognosis following complete resection, the authors do not recommend adjuvant chemotherapy for GISS. Palliative chemotherapy and/or radiotherapy may be indicated in selected patients, although there was no evidence of survival benefit in the two patients with metastatic disease in the present series who were treated with chemotherapy.

In summary, GISSs are rare tumours, originating in pleuripotent mesenchymal cells. They are part of the newly categorized group of neoplasms termed GIST. Treatment involves mainly aggressive surgical resection with the goal of complete resection, which can be curative. More cases should be studied in order to evaluate the natural history, treatment and prognosis of this disease.

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Prospective evaluation of soft tissue masses and sarcomas using fluorodeoxyglucose positron emission tomography

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Background: The differentiation of soft tissue sarcoma (STS) from benign masses is difficult owing to their clinical and radiological similarities. Accurate staging is hindered by the large number of sites at which metastases may be found. This study examined the value of whole-body [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) in patients presenting with soft tissue masses.
Methods: Thirty patients with a soft tissue mass suspected to be malignant were evaluated with FDG PET. The images were evaluated qualitatively and quantitatively for uptake of FDG to determine whether benign lesions could be differentiated from malignant tumours, and for the presence of metastases.
Results: Thirty-one masses were removed from 30 patients; 12 were benign and 19 were malignant STSs. Using qualitative assessment of the FDG PET images, all the high-grade STSs (n = 12) were correctly identified, but low-grade STS (n = 7) could not be differentiated from a benign lesion. Using a quantification assessment, there was a 95 per cent sensitivity and a 75 per cent specificity in diagnosing STS. Three patients had metastases at presentation; two were correctly identified by FDG PET.
Conclusion: FDG PET has a role in distinguishing high-grade STS from low-grade or benign STS and may have a role in staging malignant tumours.

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Introduction

The management of soft tissue sarcoma (STS) requires a multidisciplinary approach and is often suboptimal owing to failure to make a diagnosis before surgical excision. This may lead to inadequate excision margins requiring further surgery, an increase in morbidity and, in some cases, a decrease in survival[1–4]. Biopsy remains the most specific method for the diagnosis of STS but is not always performed[2]. Occasionally biopsies are not diagnostic, which can significantly prejudice subsequent treatment[3,4].

Accurate staging at presentation is essential as metastases are present in 10–23 per cent of patients. The lung is the commonest site, accounting for one-third of all metastases at presentation[5,6]; other sites include bone, liver, regional lymph nodes and retroperitoneum. Although thoracic computed tomography (CT) will satisfactorily identify lung metastases[7], multiple imaging techniques are required to exclude metastases at other sites. Nuclear imaging of the whole body has been attempted with a variety of tracers, including gallium-67[8–11], thallium-201[12,13], technetium-99m-radiolabelled hexakis-2-methoxyisobutylisonitrile and technetium-99m-radiolabelled pentavalent dimercaptosuccinic acid[14,15], with variable success.

The use of the positron-emitting glucose analogue [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) with whole-body positron emission tomography (PET) improves the cost effectiveness of staging in the management of non-small cell lung carcinoma[16] and lymphoma[17]. The ability of FDG to localize STS and to differentiate high-grade STS from low-grade and benign lesions has been demonstrated in several series[18–23]. Also FDG PET has been shown in a retrospective study to identify pulmonary metastases but with a lower sensitivity than thoracic CT. In addition, metastases were located at other sites which would not normally have been identified at presentation[24].

The three aims of this study were to assess whether FDG PET can differentiate benign from malignant soft tissue lesions using visual and semiquantitative analysis, whether the distribution of FDG uptake within the lesion could be used to identify the most malignant areas within the mass, and to assess whether whole-body FDG PET could identify sites of metastatic disease.

Patients and methods

Consecutive patients who presented with soft tissue masses that were considered to be malignant on clinical examination and magnetic resonance imaging (MRI) underwent FDG PET. The diagnosis of a malignant soft tissue tumour was based on a mass with a diameter greater than 5 cm and/or situated deep to the deep fascia. Following FDG PET, an open biopsy of the mass was done to confirm the diagnosis. Patients with a STS then underwent spiral CT of the chest to look for metastases, followed by the most appropriate definitive surgical excision of the mass. The STSs were graded histologically as low, intermediate or high as defined by Trojani *et al.*[25]. Subsequent follow-up enabled monitoring of the development of distant metastases to determine whether FDG PET had failed to identify metastases at presentation.

Fluorodeoxyglucose positron emission tomography

All patients underwent both whole-body FDG PET and separate localized views of the mass, following a 6-h fast. Data were acquired using an ECAT 951R whole-body system (Siemens/CTI, Knoxville, Tennessee, USA) in septa-extended two-dimensional mode. The scanner has an image resolution of approximately 8 mm and an axial field view of 10·8 cm (i.e. one bed position equalled 10·8 cm). A whole-body scan, not corrected for attenuation, was performed for 5 min per bed position, approximately 40 min after intravenous injection of 350 MBq FDG. Localized attenuation-corrected views of the mass were undertaken following the whole-body study using a 10-min transmission scan followed by a 15-min emission scan. This allowed semiquantitative calculation of the rate of FDG metabolism in the tumour. The images were displayed as coronal, sagittal and transaxial sections.

Analysis

All scans were evaluated both qualitatively by visual inspection and semiquantitatively by means of calculation of the standard uptake value (SUV). Qualitative assessment was made by an experienced senior nuclear medicine physician. The aim was to establish whether the mass was benign or malignant; if malignant, it was graded as either low (FDG uptake greater than in the surrounding soft tissue or contralateral tissue but less than liver uptake), intermediate (equivalent to the liver uptake) or high (greater than the liver uptake or a lesion with a photopenic area within the increased uptake). In addition, the distribution of uptake of FDG within the tumour was noted. Quantitative assessment was made by calculation of the SUV for the tumour with correction for the partial volume effect:

$$\mathrm{SUV} = \frac{A_{tumour} \times \mathrm{P}}{\mathrm{ID/BW}}$$

where A_{tumour} is the tumour activity concentration (megabequerels per millilitre), ID is the injected dose of FDG (megabequerels), BW is the body-weight (grams) and P is an experimentally determined partial volume correction.

The whole-body FDG PET scans were also assessed for the presence or absence of metastases. All scans were reported blind, without knowledge of the MRI or CT results, and before a definitive histological diagnosis.

Results

Thirty patients were assessed prospectively, 17 men and 13 women, with 31 masses. Twelve lesions were benign and 19 were STSs. The mean age of the patients was 51 (range 6–85) years. Patients with STS had a mean age of 57 years compared with 42 years for those with benign lesions. There were six different benign and eight different malignant pathological diagnoses (*Table 1*). Of the 19

Table 1 Tumour types

Tumour type	No.
Benign	
Ganglion	2
Post-traumatic fibrous tissue	3
Extra-abdominal desmoid tumour	1
Schwannoma	1
Lipoma	4
Myositis ossificans	1
Total	12
Soft tissue sarcoma	
Fibromyxoid sarcoma	1
Malignant peripheral nerve sheath tumour	3
Synovial sarcoma	2
Leiomyosarcoma	5
Pleomorphic sarcoma	2
Myxofibrosarcoma	3
Liposarcoma	2*
Alveolar rhabdomyosarcoma	1
Total	19

*One low grade and one high grade

STSs, seven were classified as low grade and 12 as high grade. There were no intermediate-grade STSs. The thigh was the commonest site for both the benign masses and the STSs (*Table 2*). The mean follow-up, including to death, of the patients with STS was 15 (median 17, range 5–29) months. Two of the 30 patients did not have whole-body scans owing to technical problems; both had high-grade tumours.

Qualitative assessment

Qualitative interpretation of the FDG PET images of the 12 benign tumours suggested that seven were benign, five of which showed no uptake of FDG. In four it was not possible to determine whether the lesion was benign or malignant. One benign tumour was incorrectly diagnosed as a low-grade STS. All of the benign tumours that accumulated FDG demonstrated a uniform distribution of FDG within the tumour.

Of the 19 malignant tumours, 17 were thought to be malignant. All of the high-grade sarcomas were diagnosed correctly. None of the benign tumours was diagnosed as high-grade STS. One STS was diagnosed as either a low-grade STS or a benign tumour, and one (a well differentiated adipocyte liposarcoma) was incorrectly diagnosed as a benign tumour. The benign tumours were not significantly smaller than the malignant lesions (mean size 6·7 *versus* 8·9 cm respectively). Thus qualitative assessment of the FDG PET scans gave a sensitivity of 95 per cent (18 of 19) with a specificity of 58 per cent (seven of 12) for the differentiation of STS from benign tumours.

Table 2 Site of tumours

Site	Benign tumours	Soft tissue sarcomas
Thorax	0	1
Groin	1	1
Buttock	0	1
Thigh	8	10
Knee	0	2
Leg	1	1
Shoulder girdle	1	0
Arm	0	1
Elbow	0	1
Forearm	1	1
Total	12	19

Quantitative assessment

The mean time after FDG injection to calculation of the SUV was 110 (median 105, range 35–214) min. The extreme time was in a patient who had neurofibromatosis type 1 with multiple lesions and in whom two static scans were performed on two different masses. The mean SUV with a partial volume correction for the benign masses was 1·35, significantly less than for STSs of 6·91 ($P < 0{\cdot}001$, Mann–Whitney U test (*Table 3*). There was a significant difference between the values obtained for the different grades of STS, and for benign tumour *versus* low-grade STS ($P < 0{\cdot}05$).

Using a cut-off SUV value of 2·0, the sensitivity and specificity for the differentiation of benign from malignant masses was 95 per cent (18 of 19) and 75 per cent (nine of 12) respectively.

Uniformity of fluorodeoxyglucose uptake compared with histological assessment

The uptake of FDG within the tumour masses was uniform or absent in all benign tumours. There was uniform FDG uptake in the low-grade STSs, which corresponded with the histological homogeneity of these tumours. FDG uptake was markedly heterogeneous in ten of the 12 high-grade lesions showing areas of photopenia within the tumours. On histological examination, all ten tumours showed areas of necrosis and of variable cellularity (*Fig. 1*). The two high-grade tumours with a homogeneous uptake of FDG, a synovial sarcoma and a leiomyosarcoma, showed no significant areas of necrosis, although there was variable

Table 3 Standard uptake values with partial volume correction for the different tumour types

		Soft tissue sarcomas		
	Benign tumours	All	Low grade	High grade
Mean	1·35	6·91	2·62	9·42
Median	1·05	4·63	2·50	6·25
Minimum	0·29	1·04	1·04	2·51
Maximum	3·14	31·91	4·63	31·91
95 per cent c.i.	0·79–1·90	3·26–10·57	1·64–3·60	3·91–14·93
P versus benign*		< 0·001	< 0·05	< 0·0001
P versus low grade*				< 0·01

c.i., Confidence interval. *Mann–Whitney *U* test

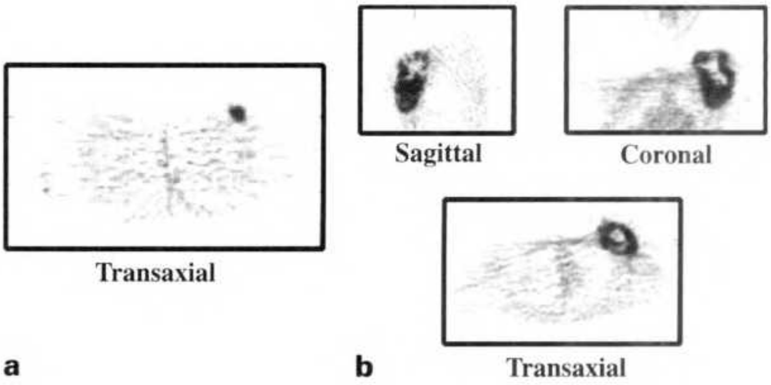

Fig. 1 High homogeneous uptake in **a** a high-grade synovial sarcoma, compared with the more usual heterogeneous uptake of [^{18}F]2-fluoro-2-deoxy-D-glucose in a high-grade soft tissue sarcoma as shown in **b** a myofibrosarcoma with a large area of central necrosis

cellularity on histological examination (*Fig. 1*). It is reasonable to conclude that the heterogeneity of FDG uptake in these tumours reflected their histological heterogeneity and significant areas of necrosis.

Detection of metastases

Twenty-eight of the 30 patients had whole-body scans. Of the ten patients with high-grade STS, three had distant metastases at presentation and one had multiple primaries. The latter patient had nine primaries and suffered from neurofibromatosis type 1. These tumours showed differences in FDG uptake. Two of these tumours were specifically investigated with localized views to allow the SUV to be calculated. Both were malignant peripheral nerve sheath tumours; one was high grade and the other low grade. FDG PET correctly identified both these tumours as malignant and graded them correctly (*Fig. 2*).

FDG PET correctly identified two of the three patients with metastases at presentation. In a patient with an alveolar rhabdomyosarcoma located in the proximal body of gastrocnemius, FDG PET identified a satellite lesion in the soft tissue of the ipsilateral proximal popliteal fossa, and metastases in the ipsilateral iliac crest and within the lungs (*Fig. 3*). Spiral CT of the chest confirmed the two metastases in the right middle zone but identified additional metastases, in the right lower lobe and within the left lung. The second patient with metastases had a high-grade leiomyosarcoma in the thigh. FDG PET identified metastases in the right lung base and mediastinum and in the left upper and lower zones, adjacent to the pleura. This was confirmed at CT, and no additional sites were identified. FDG PET failed to diagnose the presence of multiple bony metastases in the long bones and spine in a third patient with a high-grade leiomyosarcoma. Plain radiographs of the left femur (the primary tumour was

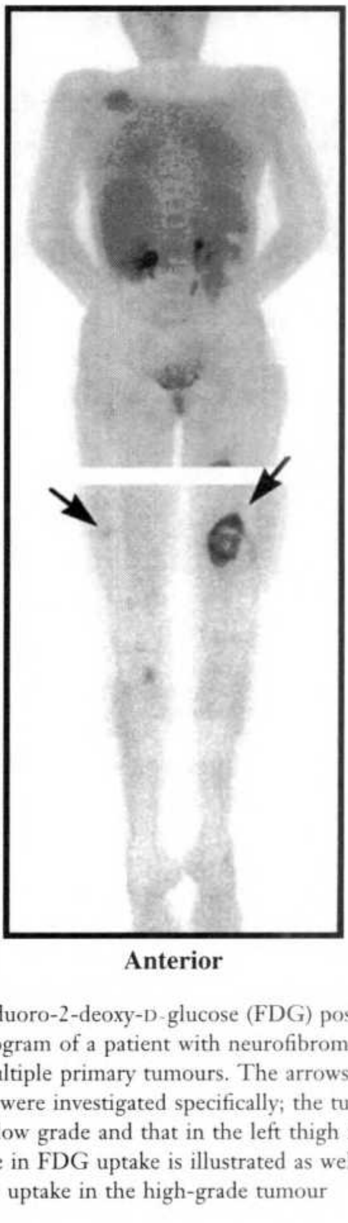

Fig. 2 [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomogram of a patient with neurofibromatosis type 1, illustrating multiple primary tumours. The arrows identify two sarcomas that were investigated specifically; the tumour in the right thigh is low grade and that in the left thigh is high grade. The difference in FDG uptake is illustrated as well as the heterogeneous uptake in the high-grade tumour

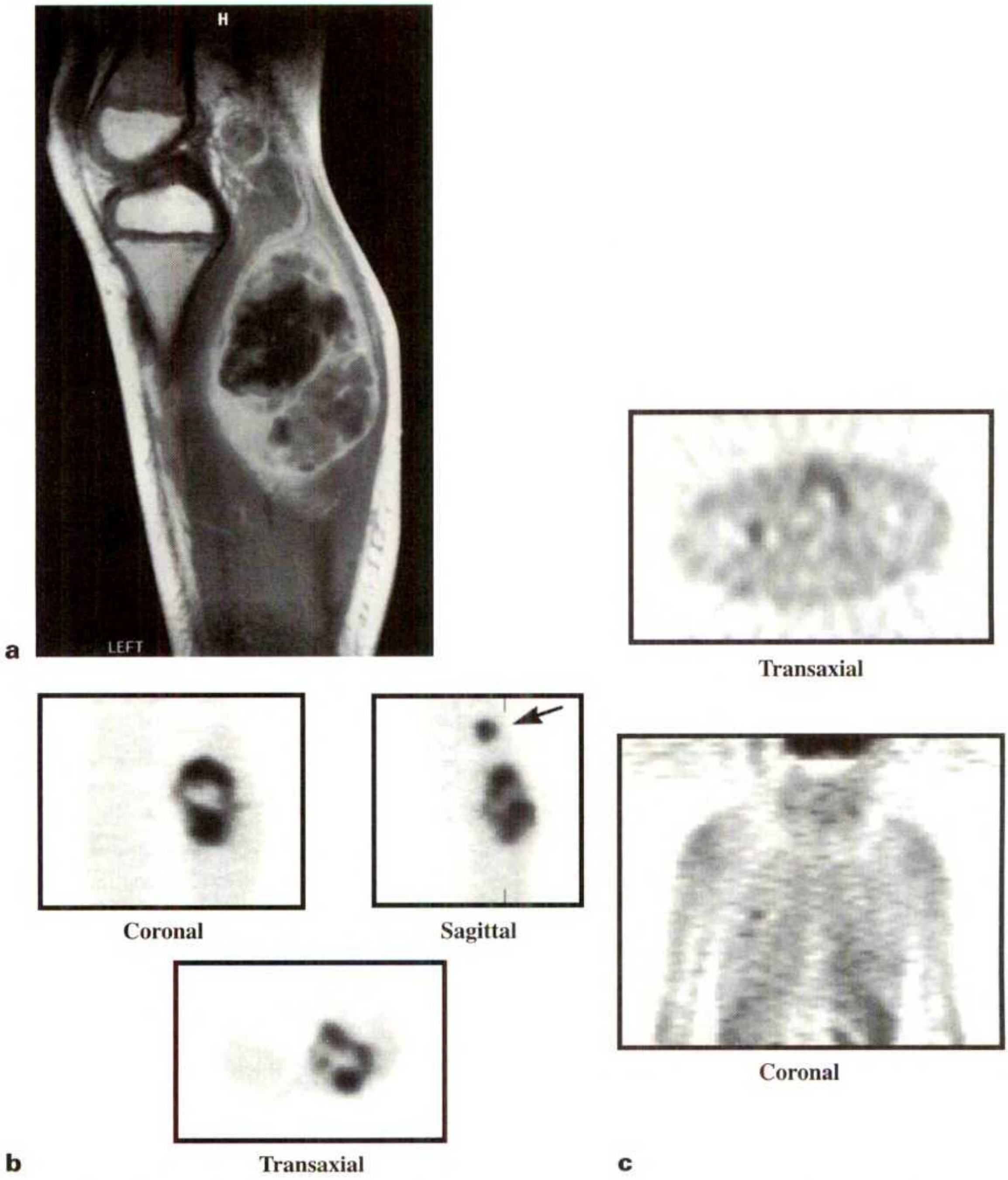

Fig. 3 Imaging of a patient with an alveolar rhabdomyosarcoma. **a** The sagittal magnetic resonance image and **b** the localized [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) image show the tumour with a satellite lesion (arrow). **c** FDG PET of the chest demonstrates two metastases

located in the left thigh) at presentation showed no evidence of metastases; however, MRI at 6 weeks' follow-up showed multiple metastases in the left femur and spine.

The remaining six patients with high-grade STS were followed for a mean of 16 (range 5–29) months. Two patients died, one from a myocardial infarction 5 months after presentation with no evidence of metastases. The other patient died at 15 months after presentation from lung metastases that were diagnosed at 1 year, with no evidence of metastases on CT at presentation. None of these patients had evidence of metastases after a minimum of 12 months' follow-up.

The patients with low-grade STS were followed for a mean of 16 (range 9–25) months. None developed metastases.

In summary, FDG PET identified the presence of metastases correctly in two of the three patients affected, and correctly identified the multiple primaries in a patient with neurofibromatosis. There were no false positives.

Discussion

The diagnosis of STS is difficult[1] and management of these tumours may best be undertaken in specialist centres. MRI is the best imaging method for STS, but has a low specificity for the differentiation of benign from malignant tumours[26–29]. A biopsy that obtains sufficient tissue representative of the mass is the only absolute method by which a preoperative diagnosis of a soft tissue tumour can be made. This is increasingly important owing to the increasing use of adjuvant chemotherapy and radiotherapy particularly before operation. However, definitive biopsy is not always achieved. Mankin *et al.*[3,4] reported an overall biopsy diagnosis error rate of 18 per cent on two separate occasions in 1982 and 1996.

PET is a new technology which has already been shown to benefit the management of a number of cancers[16,17]. The availability of PET technology has increased in most developed countries. The modification of a γ camera to operate in dual coincidence mode also potentially opens up the imaging of positron-emitting radionuclides to a wider group of clinicians.

In this study semiquantitative analysis of FDG PET images was able to differentiate high-grade STS from benign masses or low-grade malignancy with a sensitivity of 95 per cent. This distinction contrasts with a recently published report where there was significant overlap between low- and high-grade tumours[23]. This may have been due to a difference in the timing of the scans, since previous calculation of SUVs was derived from scans taken between 20 and 60 min after injection, whereas in the present study scans were obtained at a median time of 105 min. The simulated uptake of FDG may not peak until 5 h after the injection of FDG[30]. A similar timing problem may apply to STS. It is possible that extending the time at which the SUV is measured may improve separation of benign from malignant tumours and the distinction between benign lesions and low-grade malignancy. In high-grade malignancies, FDG PET might be capable of monitoring the effectiveness of neoadjuvant and adjuvant therapies.

The heterogeneous uptake in high-grade sarcomas, which corresponded to histological areas of necrosis and variable cellularity, was demonstrated in scans from the present study (*Fig. 1*). Identification of such areas may be helpful for determining the optimum site of a biopsy.

FDG PET detected the presence of lung metastases in two patients, but metastases at other sites within the lungs were identified by CT. Again the time lapse between injection and the scan may have been too short to allow accumulation of the FDG within smaller metastases. Likewise FDG PET identified bony metastases in one patient but failed in another.

In the present study FDG PET was capable of distinguishing between high-grade STSs and benign lesions. However, distinction of low-grade tumours from benign disease was unsatisfactory. The distribution and intensity of uptake had potential value in directing the surgeon to biopsy the most malignant areas of the tumour. Whole-body PET at first presentation with thoracic CT should identify most sites of metastatic disease. With improved understanding of the kinetics of FDG uptake, the sensitivity for detection of metastases may be improved.

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Appropriate use, complications and advantages demonstrated in 500 consecutive needle catheter jejunostomies

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Background: The ability to deliver nutrition enterally after operation has been a significant advance in managing patients after major intra-abdominal operations.

Methods: The experience of a single surgeon at a tertiary referral hospital over a 10-year period with insertion and use of 500 consecutive needle catheter jejunostomies (NCJs) was reviewed critically from prospectively collected data.

Results: The NCJ was used to deliver nutrition in 93 per cent, fluid and electrolytes in 95 per cent, and various medications in the postoperative period in the majority of patients. There were three major complications: small bowel obstruction and pneumatosis intestinalis in one and two patients respectively. Minor complications included diarrhoea (15 per cent), abdominal distension (15 per cent), abdominal cramps (3 per cent), subcutaneous infection at the insertion site (1 per cent) and catheter occlusion precluding use (1 per cent). In 16 patients, the NCJ was replaced percutaneously with a larger-bore catheter for more prolonged enteral feeding at home after discharge.

Conclusion: Through the experience gained, indications are offered for the placement of NCJs and cautions are provided concerning appropriate use of an NCJ to provide nutritional support, fluid and electrolyte replacement or maintenance, and safe enteral administration of medication. Overall, an NCJ appears to allow safer, cheaper and equally effective delivery of nutrition compared with total parenteral nutrition after major intra-abdominal operations.

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Introduction

Techniques to allow enteral feeding after intra-abdominal operations have proved a significant advance in decreasing the morbidity and mortality rates associated with major intra-abdominal surgery[1,2]. Some centres have adopted needle catheter jejunostomy (NCJ) as the primary means of providing nutritional support on a short-term, in-hospital basis beginning in the immediate postoperative period. NCJ has several advantages. First, it carries fewer complications than a formal tube jejunostomy using the Witzel technique[3]. Second, NCJ allows provision of additional fluid and electrolytes (thereby often avoiding need for prolonged intravenous access). Third, NCJ permits a safe means of administering many medications that might otherwise require central venous access or monitoring if given intravenously[4].

This report outlines a decade of experience with the use of 500 NCJs, with emphasis on appropriate indications, techniques of delivery of nutritional support, other non-nutritional uses of NCJ, and recognition and avoidance of potential complications.

Materials and methods

Data were collected prospectively from all patients in whom NCJ was placed from 1985 to 1995, and included demographic data, operation performed, need for enteral nutritional support (preoperative malnutrition), complications directly related to the NCJ and its duration of use.

The technique of insertion of the NCJ has been described in depth previously[4]. In brief, a 14-G needle 7 cm long is inserted intramurally into the wall of the proximal jejunum parallel to the long axis for about 5 cm before plunging the tip of the needle into the lumen. A 16-G catheter (external diameter 1·7 mm) is then threaded through this needle into the lumen for 25 cm and the needle removed; care is taken to avoid curling or kinking of the catheter. A purse-string suture of 3/0 absorbable suture is placed around the insertion site. The opposite end of the catheter is then exteriorized through a separate sterile 14-G needle passed into the peritoneal cavity through the anterior abdominal wall. Two points in this manoeuvre are important. First, the catheter is exteriorized at whatever point the jejunum seems to easily reach the anterior abdominal wall in a gentle curve, usually in the left upper quadrant but not uncommonly in the right mid abdomen when placed distal to a gastrojejunostomy or bilioenteric anastomosis. Second, the needle passed to exteriorize the catheter should be inserted at about a 45° angle to the skin so that the catheter will exit the peritoneum directly in a straight line; if the needle enters the peritoneum at a right angle, the catheter will kink as it leaves at the exit site from the jejunum. After fixing the jejunum to the anterior abdominal wall, several more tacking sutures are placed proximally or distally to assure a broad fixation of the jejunum to the posterior surface of the anterior abdominal wall to prevent any twisting at the exit site. The catheter is fixed to the skin just distal to the exit site with a 3/0 polypropylene suture to hold it in place, then a plastic transparent adhesive dressing is placed over the catheter and butterfly needle complex to keep the entire catheter complex in place. At this time it is important to flush the catheter to be certain that there are no kinks or occlusion. If flushing is not possible, pulling the catheter out 1 or 2 cm usually relieves any kinks that might be present in the catheter either within the bowel or within the abdominal wall.

Several commercially available kits that use larger-diameter catheters (more than 16 G) have been tested but were found to be unsatisfactory because of the difficulty in inserting the catheter within the wall of the jejunum without 'fracturing' the intramural tract or otherwise causing undue damage to the jejunal wall.

The protocol for enteral nutrition calls for starting feeding with a quarter-strength solution (full-strength solution diluted three times with water) at 25 ml/h in the morning of the first day after operation; electrolytes and/or medication are often given enterally immediately after operation, but it is usually more convenient to begin the infusion the next morning. The rate of delivery of enteral feed is increased by 25 ml/h every 12 h until the target volume is reached (e.g. 100 ml/h for a 70-kg patient); then the strength (osmolality) of the solution used is increased every 12 h from one-quarter to one-third, then to one-half and finally to a strength of two-thirds. This protocol appears to minimize the incidence of diarrhoea and/or cramps associated with beginning intrajejunal infusion of full-strength solutions even at low rates. Limiting the strength to no greater than two-thirds appears to minimize the incidence of catheter occlusion. When diarrhoea, severe cramping or abdominal distension develops, feeding is stopped and replaced with isotonic saline (0·9 per cent sodium chloride) for 8 h, and then restarted after adding six drops of deodorized tincture of opium per 500 ml enteral nutrition solution.

Non-elemental formulae are preferred because these solutions are cheaper, well tolerated by patients and equally effective. However, an elemental solution is used in the event of pancreatic exocrine insufficiency or proximal diversion of bile and/or pancreatic exocrine secretions or during treatment with a somatostatin analogue.

The NCJ was used routinely to deliver additional water and electrolytes to meet daily requirements or replace gastrointestinal losses such as nasogastric or biliary secretions. Pancreatobiliary secretions can be reinfused through the NCJ after straining out any particulate matter. Medications absorbed in the small intestine were also given by the NCJ whenever possible. Every attempt was made to administer a liquid preparation of the medication; otherwise the tablet or pill was crushed and diluted in 10–20 ml of water. The NCJ was diligently flushed clear with water thereafter.

Results

Patients

The NCJ was placed after a gastro-oesophageal procedure in 74 patients (15 per cent), after a complex bariatric procedure in 139 (28 per cent), after elective pancreatobiliary resection in 41 (8 per cent) and after other complex upper or lower gastrointestinal procedures in 246 patients (49 per cent) for both benign and malignant diseases.

Nutritional support

A total of 464 patients (93 per cent) underwent infusion of intrajejunal nutrition. There were varying degrees of nutritional need ranging from complete nutritional support in the preoperatively malnourished patient (approximately 10 per cent of the patients in this series) to the otherwise healthy patient undergoing a major operation managed by nutritional maintenance to support healing early after operation before resuming oral intake. If a patient needed nutritional support in the immediate postoperative period, an NCJ was placed whenever possible. The majority of patients had the NCJ placed largely as a prophylactic measure after high-risk procedures in case a postoperative complication precluded oral intake.

A non-elemental diet was used in 412 patients (89 per cent) and an elemental diet in the other 52 (11 per cent).

The mean(s.d.) number of calories delivered per 24 h was 1350(25) (range 0–3200) kcal and it took 3·9(0·1) days to reach the target rate. Enteral feeding was delivered for a mean(s.d.) of 12(1) (median 10, range 1–180) days. Sixteen patients were discharged home on enteral feeding having had the 16-G NCJ changed to a 4-, 6- or 8-Fr feeding tube using a Seldinger technique.

Fluid and electrolyte maintenance or replacement

Some 475 patients (95 per cent) had the NCJ used to deliver all required maintenance and replacement fluid and electrolytes. It took a mean(s.d.) of 3·9(0·1) days to reach the rate of fluid and electrolytes necessary to allow the intravenous catheter to be removed.

Medication

A range of medications was administered, from potassium replacement in 142 patients (28 per cent) to histamine-2 receptor antagonists in 353 (71 per cent) and analgesics in 218 (44 per cent). Certain cardiotonic agents, including β-adrenergic agonists in 34 patients (7 per cent) and antiarrhythmics in 27 (5 per cent) were given by NCJ. Aminophylline was given by NCJ in six patients (1 per cent). Many other miscellaneous agents were also given, including metoclopramide, digoxin, synthroid, anti-emetics and coumadin.

Complications (*Table 1*)

Major complications

There were no instances of intraperitoneal leakage of intraluminal content, intraperitoneal delivery of enteral nutrition solution, intestinal necrosis or intra-abdominal abscess related to the NCJ. One patient developed a small bowel obstruction around the site of the NCJ. Two patients developed abdominal distension secondary to pneumatosis intestinalis; both were managed successfully by stopping the enteral feeding and resuming it several days later when the abdominal distension had settled.

Table 1 Complications of needle catheter jejunostomy in 500 patients

	No. of patients
Major	
Small bowel obstruction	1 (0)
Pneumatosis intestinalis	2 (0)
Minor	
Diarrhoea	75 (15)
Treatment required	55 (11)
No treatment required	20 (4)
Distension	25 (5)
Cramps	13 (3)
Occlusion (permanent)	3 (1)
Dislodgement	1 (0)
Subcutaneous infection	7 (1)

Values in parentheses are percentages No patient developed a leak at the insertion site or intestinal necrosis

Minor complications

Diarrhoea (more than four liquid bowel movements per day) developed in 75 patients (15 per cent) and required treatment with enteral opiates in 55. Significant cramps or abdominal distension requiring temporary discontinuation of enteral feeding developed in 3 and 5 per cent respectively. One patient had the NCJ dislodged permanently (a confused elderly patient) and three patients developed occlusion of the NCJ preventing its use. Seven patients developed a subcutaneous abscess or cellulitis at the skin insertion site, five of whom required incision and drainage.

Discussion

This experience with 500 consecutive NCJs confirms their safety when used appropriately. In addition to providing a safe, effective route for delivering enteral nutrition distal to the stomach and duodenum, the NCJ can be used to administer water, electrolytes, almost all types of medication normally given orally and many other agents that would require parenteral administration in the patient unable to ingest them orally; use of this enteral route saves nursing time and reduces costs.

Many abdominal surgeons are reluctant to use a percutaneous enteral route for fear of major mechanical complications related to the tube jejunostomy[3]. There was no leak or intraperitoneal sepsis in the current series and only one patient had a bowel obstruction related to the NCJ. While it is acknowledged that nasojejunal tubes avoid these complications, nasojejunal tubes are much less well tolerated by the patients both subjectively and from a respiratory standpoint.

Others have reported rare but serious complications related to enteral feeding. Small intestinal necrosis or pneumatosis intestinalis have been reported in 0·15–3 per cent of patients[5–8]. Both complications are thought to be related to the osmolality of the enteral solution. There was no case of intestinal necrosis but two patients in the present series developed pneumatosis intestinalis[9], both of whom recovered with non-operative management. The low incidence of these complications may be due to the low osmolality of the solution delivered when an NCJ is placed either prophylactically or for reasons other than nutritional need (see below).

Several studies have suggested that enteral and parenteral delivery of nutritional support are equal in terms of eventual delivery of calories[10–13]; however, more recent detailed studies examining other aspects of nutritional support have demonstrated the superiority of enteral nutrition[14–21]. Advantages of enteral nutrition include reduced costs and, more importantly, a lower incidence of intra-abdominal and systemic sepsis[15,20,21]. The latter is presumably related to preservation of the mucosal barrier by the presence of enteric nutrients[14,19,22,23] and maintenance of immune function[14,18,19].

This experience with early nutritional support has been good. Although some groups[24–26] describe a high incidence of intolerance to enteral feeding secondary to diarrhoea, cramps and abdominal distension, the author's experience and that of others[2,21] has been much different. Diarrhoea requiring treatment or discontinuation of feeding occurred in only 11 per cent of the present patients, while cramps or distension required discontinuation of enteral nutrition in only 8 per cent. While others start postoperative feeding with a full-strength solution at slow rates (20 ml/h) and then slowly increase the rate, the author's success with enteral feeding is believed to be related to the approach of starting with a low concentration of the feeding solution and increasing the effective osmolality only after the target rate is reached. This approach minimizes diarrhoea and allows early discontinuation of maintenance intravenous water and electrolytes.

Although NCJ was developed for short-term early postoperative enteral feeding, techniques exist for converting the small-bore catheter to a larger catheter for long-term use[27]. Using guidewire dilators and a peel-away sheath, progressively larger catheters (4–8 Fr) can be introduced through the tract of the 16-G NCJ; these larger catheters will minimize catheter occlusion during home enteral nutrition. This was done in 16 patients to allow long-term enteral nutritional support after discharge from hospital.

A less well appreciated benefit of the NCJ is the ready access for delivery of water, electrolytes and most medications. An NCJ is occasionally placed in selected patients with limited vascular access, especially if a high-risk central vein puncture is going to be required[28]. Similarly, many routine medications, including analgesics, gastric antisecretory agents, antiemetics and diuretics, can be delivered enterally. Equally important is the ability to deliver medications that cannot be given intramuscularly or would otherwise require intravenous administration with monitoring in an intensive care unit.

Avoiding some of the minor problems of the technique of NCJ requires several insights into their use. Exteriorizing the catheter through the abdominal wall at a 45° angle prevents kinking at its entrance into the peritoneum. Similarly, when there appears to be an occlusion within the proximal section of the catheter within the abdominal wall, pulling the catheter back several centimetres often reveals a kink and relieves the obstruction. Administration of medication in liquid form is preferable to using a crushed tablet. Using an enteral nutrition solution at two-thirds strength minimizes catheter occlusion and mechanical problems with the pump regulating the infusion. When occluded, forceful flushing with a small (1 or 3 ml) syringe and passage of a flexible-tip guidewire can usually unblock an occluded catheter. A short educational seminar given to the nursing staff can help to prevent these annoying problems.

In summary, the following indications for placement of an NCJ are suggested: (1) high-risk operations that because of related complications, e.g. gastroparesis, upper-gut anastomotic leak, would preclude orally delivered nutrition; (2) need for early nutritional support; (3) limited vascular access requiring prolonged central venous access or an otherwise unnecessary high-risk central venepuncture; and (4) need for specific cardiotonic, respiratory or antiepileptic drugs which are difficult to administer parenterally.

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Chronic groin sepsis following tension-free inguinal hernioplasty

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Background: Chronic groin sepsis requiring mesh removal is said to be a rare complication of tension-free inguinal hernioplasty. The aim of this study was to determine the number of surgeons performing tension-free inguinal hernioplasty in the West of Scotland and assess the frequency with which chronic groin sepsis was encountered.

Methods: A questionnaire was sent to all consultant surgeons performing inguinal hernia repair in the region and follow-up of patients with chronic groin sepsis following tension-free inguinal hernioplasty was undertaken.

Results: Of 80 consultants who replied to the questionnaire, 79 were performing tension-free hernioplasty. Of these, 76 were performing only open repairs while three were also undertaking laparoscopic repairs. Sixteen consultants reported 20 patients with groin sepsis after mesh repair. Twelve patients were traced; eight had chronic sinuses and four had groin abscesses. The median interval between repair and presentation was 4 months (range from 2 weeks to 39 months). All have required complete (11 patients) or partial (one) removal of mesh to resolve the symptoms.

Conclusion: Tension-free inguinal hernioplasty has become the operation of choice for surgeons in the region. Chronic groin sepsis may be more frequent than reported previously. Complete removal of mesh is required to treat this condition.

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Introduction

The use of prosthetic material for inguinal hernia repair has increased dramatically since first described by Giraud and colleagues[1] using a nylon mesh in 1951. Various meshes have since been developed consisting mainly of non-absorbable materials, such as polypropylene, polyester and polytetrafluoroethylene. The presence of a plastic biomaterial raises the possibility of complications relating to the mesh itself as well as the recognized complications from the hernia repair. This includes mesh infection resulting in chronic groin sepsis, the true incidence of which is unclear.

The aim of this study was to determine the number of surgeons performing tension-free inguinal hernioplasty in the West of Scotland and to assess the frequency with which chronic groin sepsis was encountered by these surgeons.

Patients and methods

All consultant surgeons performing inguinal hernia repair in 19 hospitals in the West of Scotland were sent a questionnaire asking whether they performed open or laparoscopic tension-free hernioplasty for primary or recurrent groin hernias. They were also asked whether they had encountered chronic groin sepsis and, if so, what type of mesh was involved. Once a patient had been reported, the consultant was contacted to determine whether he or she could remember details of the case. Hospital records were then obtained for each patient to confirm the accuracy of the report and to examine other factors such as infecting organism, the number and types of treatments and whether the mesh was partially or completely removed.

In addition, the patient's general practitioner was contacted to confirm the timing of the first consultation with symptoms following hernia repair, and to ensure that no problems had arisen since the mesh was removed or the last operation was performed.

Results

Eighty of 83 consultants replied to the questionnaire of whom 79 (99 per cent) were performing tension-free hernioplasty; only three were also undertaking laparoscopic repairs. Sixteen consultants indicated that they had experience of 20 patients with chronic groin sepsis. Of these it was possible to obtain accurate details in 12, all of whom underwent hernia repair between July 1993 to September 1997. Eleven underwent open tension-free hernioplasty using the Lichtenstein method while one had a transabdominal laparoscopic repair of bilateral hernia. There were 11 men and one woman with a median age of 47 (range 23–76) years. The operations were performed or supervised by consultant surgeons in eight of the 12 repairs. Although all surgeons stated that they used antibiotic prophylaxis, documented evidence of antibiotic use could be found for only one patient. The type of mesh utilized in the repair was Surgipro (AutoSuture, Ascot, UK) in nine patients, Marlex (C. R. Bard, Billerica, Massachusetts, USA) in two and Prolene (Ethicon, Edinburgh, UK) in one. Apart from two patients who developed superficial wound infections on days 5 and 6 after operation, no other immediate postoperative complication occurred in any patient.

Presentation

The median interval between repair and presentation to hospital was 4 months (range from 2 weeks to 39 months). At the time of presentation eight patients had chronic groin sinuses while four had groin abscess. Bacterial isolates were obtained in 11 patients. In ten, *Staphylococcus aureus* was grown from swab culture, with one groin infection also producing such diverse organisms as *Proteus* species, group B streptococci and *Peptostreptococcus*. One patient grew anaerobes (Gram-positive cocci and Gram-negative bacilli) from blood culture. An organism was isolated in less than 50 per cent of swabs taken.

Management

Management is summarized in *Fig. 1*. Eleven of the 12 patients were initially treated with antibiotics, whereas one had the mesh removed at first presentation. Flucloxacillin was the most common antibiotic prescribed with erythromycin, ciprofloxacin, amoxycillin–clavulanic acid (Augmentin; SmithKline Beecham, Welwyn Garden City, UK) and metronidazole being used less frequently. All

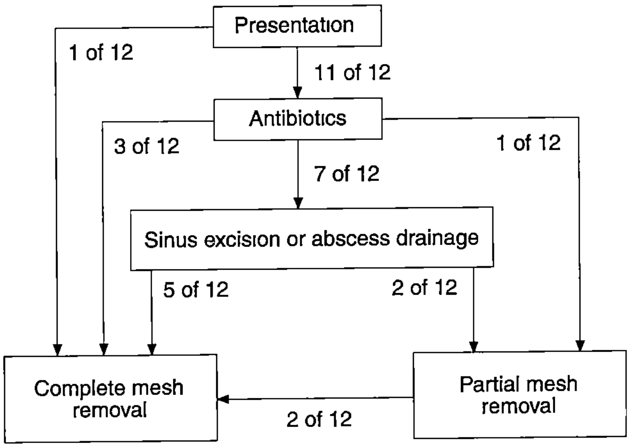

Fig. 1 Summary of patient management

patients with a groin abscess had incision and drainage, whereas three with a sinus had exploration with partial mesh removal. Two of these three developed recurrent sinuses and have since proceeded to complete mesh removal. Eleven further patients have had complete mesh removal. In all, the 12 patients have had 23 operative procedures. At operation, the mesh was usually found floating in pus encased with a fibrous surrounding capsule.

Follow-up

Of 11 patients for whom follow-up data are available, two have developed a recurrent hernia, one of whom is asymptomatic and currently under observation. The other, who had previous bilateral laparoscopic repair, required an open tension-free hernioplasty for a right-sided recurrence. Although this operation took place 2 years after mesh removal, the patient developed a further episode of chronic groin sepsis which again required removal of the mesh to resolve the symptoms.

Discussion

Chronic groin sepsis requiring mesh removal is seen as a rare complication of tension-free hernioplasty, with Shulman *et al.*[2] reporting no cases in more than 3019 open tension-free hernioplasties. This contrasts with the experience of Furtschegger *et al.*[3], who found two cases of mesh infection in 1139 laparoscopic hernia repairs, whereas others have reported the problem in both laparoscopic[4] and open[5] hernia repair.

The West of Scotland has a population of 2·25 million, of which approximately 3400 adults undergo groin hernia repairs each year. Based on 12 confirmed cases of chronic groin sepsis following tension-free hernioplasty over a

4-year period, this would indicate that sepsis occurred in one in every 1100 cases in this study. This is a conservative estimate, however, as surgeons reported a further eight patients who could not be traced, and it is unlikely that all patients with a groin hernia had a mesh repair during the study period.

The different physical structures of polypropylene mesh may be important in chronic groin sepsis. This study identified three types of polypropylene mesh being used in the area: a multifilament mesh (Surgipro), a monofilament mesh (Marlex) and a dual-filament mesh (Prolene). Multifilament mesh has a closer weave structure with a smaller pore diameter (10 μm) than monofilament or dual-filament polypropylene mesh (greater than 75 μm). This can allow bacteria of 1 μm in diameter to penetrate but exclude the penetration of polymorphonuclear leucocytes (diameter greater than 10 μm) and thus shield the bacteria from immunological attack[6]. Multifilament strands may allow greater bacterial adherence between the braids and may be less resistant to bacterial contamination[7]. Use of multifilament suture has also been suggested as the source of contamination with monofilament polypropylene meshes[6]. The reason for the wide variation in time to presentation is unclear. Whereas cases that presented early are likely to be due to contamination at the time of implantation of the mesh, in those presenting at 2–3 years contamination from an endogenous source needs to be considered, as in the haematogenous infection of joint prostheses from chronic skin lesions[8].

The striking feature in these patients was the failure of conservative treatments such as sinus excision and abscess drainage. There is, however, no clear consensus on the management of mesh infection because of its rarity, so attempts at conservative management before proceeding to mesh removal can be understood. Successful resolution of symptoms with sinus excision and leaving the mesh *in situ* has previously been found with Marlex[5] and Prolene[9]. When partial mesh excision is undertaken, the remaining mesh probably has residual contamination, as the mode of bacterial spread on implants is in a horizontal adherent manner along its surface[10]. This may not be readily apparent at operation, and interim procedures generally prolong the time before complete mesh removal is undertaken, which in this series was the only treatment that resolved the infection effectively. The only individual who had partial mesh removal had a short follow-up (7 months) and may still 'relapse'.

In the presence of established infection antibiotics are probably ineffective for a number of reasons. The thick fibrous capsule surrounding the infected mesh is likely to limit antibiotic penetration into the site of sepsis. *S. aureus*, the most common infecting organism, is known to produce a biofilm on adherence to a biomaterial, which shields it from both immune cells and antibiotic therapy[11]. This biofilm also results in a low identification rate of organisms from swab analysis or from the mesh itself[12]. Finally there may also be a localized defect of polymorphonuclear leucocyte function at the mesh interface resulting in frustrated phagocytosis when biomaterials are involved[13]. Antibiotic prophylaxis has not been proven to alter wound infection rates in inguinal hernia surgery[14], and it is difficult to rationalize antibiotic use against late mesh infection. The effect of topical antibiotics and other antibacterial agents is unclear.

Although rare, chronic groin sepsis secondary to mesh infection may be more common than previously reported. When chronic sepsis does arise, the present experience suggests that swab analysis is unreliable, and that antibiotics and mesh-saving operations are ineffective. Complete mesh removal should be attempted at an early stage and incomplete removal should be suspected if symptoms recur. Consideration should be given to a sutured hernia repair for any symptomatic hernia recurrence that develops following mesh removal for chronic groin sepsis.

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External oblique aponeurosis nerve entrapment as a cause of groin pain in the athlete

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Background: Groin pain in sportsmen is a common management problem. The results of surgical exploration in 25 male athletes presenting with groin pain are described.
Methods: All patients had had failed non-operative management. All groins were explored via an inguinal incision and the patients were reviewed for the presence of pain, function and their own subjective opinion.
Results: Nineteen injuries were unilateral and six bilateral. One patient had an occult inguinal hernia and another had a patent processus vaginalis. In the others, defects were found in the external oblique aponeurosis through which neurovascular bundles containing terminal branches of the iliohypogastric nerve passed. These tears were repaired after division of the bundles. The mean time to referral was 29·3 weeks (range 4–79 weeks). After operation no pain or only mild pain was experienced in 28 groins. All had improved function. Twenty of 23 patients described the operation as good or excellent. The mean time to resumption of sporting activities after operation was 11·6 (range 4–20) weeks.
Conclusion: Athletes' groin pain may be due to nerve entrapment in the external oblique aponeurosis. An awareness of this injury may reduce delays in operating leading to an earlier return to sport.

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Introduction

Sporting injuries affecting the groin can present a problem in both diagnosis and subsequent management. A number of injuries, such as musculotendinous strains and tears, readily settle with conservative treatment. However, some groin injuries will require operation, such as disruption of the posterior wall of the inguinal canal or the sportman's hernia, which describes a significant weakness or derangement of the posterior wall of the inguinal canal. Open repair with either Bassini or nylon darn techniques results in a return to full sporting activity in 62–93 per cent of athletes with this problem[1–4].

Gilmore[5] described a triad of features: torn external oblique aponeurosis causing external ring dilatation, torn conjoint tendon, and dehiscence between the inguinal ligament and conjoint tendon. Repair of this disruption including a nylon darn resulted in 97 per cent return to professional football within 10 weeks.

Single or multiple small tears in the external oblique aponeurosis at the site of emergence of small neurovascular bundles containing the terminal branches of the iliohypogastric nerve have been described previously as a cause of groin pain in six athletes, whose groins were explored after failed conservative treatment[6]. This study presents the results of the surgical treatment and reviews the pathophysiology of this condition.

Patients and methods

Twenty-five men, with a mean age of 26·7 (range 22–37) years, were reviewed following surgical exploration of the groin for pain at a mean follow-up of 20·6 months (range 7–56) months. Fifteen presented with right groin pain, four with left-sided symptoms and six with bilateral groin problems. The principle sport in which the patients participated was rugby or football in 19 patients, and cycling, hockey, marathon running and cricket in the remaining four.

All patients were referred between February 1992 and March 1997 after failed conservative treatment such as physiotherapy and local anaesthetic and steroid injections. One patient had been treated with antidepressants. Because of persistence in treating most of these athletes non-surgically, there was a lengthy delay from the onset of symptoms to referral for a surgical opinion. The mean time from the initial injury to operation was 29·3 (range 4–79) weeks.

Characteristically the patients presented with groin pain increased by sudden movements including kicking, rolling over in bed, coughing and sneezing. On examination there was an area of tenderness just superior to the deep ring. Neither a cough impulse nor dilatation of the superficial ring was found on clinical examination.

Each patient had been investigated before operation by the referring clinician by means of radiographs of the pelvis, ultrasonography, bone scan and, more recently, magnetic resonance imaging. All of these investigations were normal.

Each affected groin was explored under general anaesthesia through an inguinal approach as used for open inguinal hernia repair. Following operation all patients were given a standardized rehabilitation programme as used by Gilmore[5] to aid recovery (*Table 1*).

With the use of a questionnaire all of the patients were asked for their subjective assessment of the operation in terms of pain, function and their overall appraisal of the procedure. The interval from surgery to a full return to sport was also recorded.

Results

Exploration of the groin revealed an occult indirect inguinal hernia in one patient and a patent processus vaginalis in another. These two patients made an uneventful recovery and returned to full sporting activities after standard treatment.

In the other 23 patients single or multiple tears 1–4 cm long were seen in the external oblique aponeurosis at the sites of the perforating neurovascular bundles, which contain the terminal branches of the iliohypogastric nerve. Following routine exploration of the inguinal canal to exclude any other pathology, these tears were repaired with interrupted nylon sutures after division of the neurovascular bundles. Repair of the transversalis fascia was not required.

There were no postoperative complications. Following repair of the tears, subjective pain was much improved (*Table 2*): no pain was experienced in 20 groins and eight had only mild pain which did not interfere with sporting activities. In only one patient was the pain not improved. However, all patients returned to sport with 20 athletes competing at the same level as before injury. This included all those who underwent bilateral exploration. Three others, who were unable to compete before surgery, returned to sport but at a lower level.

Table 1 Rehabilitation programme

Week 1	Stand upright and walk 20 min on first day after operation
	Thereafter walk gently four times each day
Week 2	Walk 30 min twice a day for 4 days
	Gentle jogging for rest of week
Week 3	Straight line running
	Gentle sit-ups
	Adductor exercises
Week 4	Sprinting in straight lines
	Increase sit-ups
	Swimming (crawl)
Week 5–6	Kick, play

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Table 2 Results of operation

	n
Pain (no. of groins)	
None	20
Mild, but improved	8
No improvement	1
Function (no. of patients)	
Returned to full sporting activities	20
Improved, but playing at lower level	3
No improvement, unable to play sport	0
Patient satisfaction (no of patients)	
Excellent	9
Good	11
Satisfactory	3
Poor	0

The mean time to resumption of sporting activities for all patients following operation was 11·6 (range 4–20) weeks. Those who underwent bilateral groin exploration had a faster return to sporting activity with a mean postoperative recovery time of 6·8 (range 4–12) weeks.

Twenty of the patients rated the result of the operation as good or excellent.

Discussion

The operative pathology seen in these patients consisted of single or multiple tears in the external oblique aponeurosis at the site of the emergence of neurovascular bundles containing the terminal branches of the iliohypogastric nerve. These tears varied from 1 to 4 cm in length. Such a tear may produce a nerve entrapment syndrome as no other pathology, such as occult hernia or a tear in the conjoint tendon as described by Gilmore[5], was found in these patients.

Surgical repair of these tears in the external oblique aponeurosis resulted in the return of all patients to sporting activities in a mean time of just over 11 weeks. The apparent faster recovery of those with bilateral injuries may be the result of a more rigorous postoperative rehabilitation as these athletes were all playing first class rugby or semiprofessional football.

Most of the athletes had prolonged unsuccessful non-surgical treatment for a mean period of over 6 months. This has been noted previously[5]. There are a number of conditions causing groin pain which can be treated conservatively with success, such as strains of musculotendinous units or inguinal ligament enthesopathy[7], but earlier recognition of surgical causes of groin pain in the athlete may reduce delays in returning to sport.

Other nerve entrapment syndromes have been described previously. Kopell *et al.*[8] described an entrapment neuropathy of the ilioinguinal nerve which causes groin pain in a similar area to that experienced by the patients in this series; entrapment of this nerve together with the genitofemoral nerve, which also causes groin pain, has been treated successfully by nerve section[9].

There are a number of other sporting injuries affecting the groin which have been reported to respond well to open surgical intervention, such as Gilmore's groin and groin disruption[1–5]. Laparoscopic mesh repair may permit an earlier return to sport than an open mesh technique[10], but this study was not randomized and laparoscopy may result in missed pathology. Other surgical causes of groin pain in the athlete include inguinal hernias; direct hernias are more common, comprising 56 per cent of cases, and these respond well to herniorrhaphy[11].

As with cases of groin disruption, investigating these athletes with radiological imaging can be fruitless. The present patients had often undergone plain radiography of the pelvis and hips, ultrasonography, bone scans and magnetic resonance imaging which, while excluding other causes of groin pain, did not show any abnormality. Herniography may be of value if a hernia is suspected[11–13], but there can be a high false-positive and -negative rate[14]. Improvements in diagnosis may be made with the use of dynamic magnetic resonance imaging, which can demonstrate sac herniation while the patient performs a Valsalva manoeuvre[15].

These findings suggest that external oblique aponeurosis entrapment of the iliohypogastric nerve is a cause of groin pain in the athlete, for which surgical treatment results in a return to sport. An awareness of this problem as well as other surgical causes of groin pain may avoid delays in resumption of sporting activities.

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The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Preoperative duplex imaging is required before all operations for primary varicose veins

Letter 1

Sir

I read with interest the paper by Mercer *et al.* (*Br J Surg* 1998; **85**: 1495–7) with a conclusion as clearly stated in the title. Apart from the practical and clinical message, there are important resource and even medicolegal implications. It is all the more important, therefore, to have confidence in the evidence on which this assertion is made. The authors kindly made reference to our own experience on this subject[1] and noted that our findings were significantly different. They do not, however, speculate as to why this might have been the case, nor indeed comment on how this variance would modify any conclusions. Our findings revealed that duplex scanning can be confined to limbs with reflux detected in the popliteal fossa on continuous wave Doppler (about 25 per cent of patients). If this policy had been pursued in the 100 limbs reported, the only operative 'errors' would have been missed coexistent short saphenous incompetence in two limbs undergoing appropriate long saphenous ligation.

The techniques employed with continuous wave Doppler in our study were quite different from those described by Mercer *et al.* and might well explain the different outcomes. In common with a number of other authors referred to in their discussion, we feel that continuous wave Doppler, when properly employed, is quite adequate to diagnose long saphenous incompetence and to identify the 25 per cent of patients with reflux in the popliteal fossa requiring more detailed duplex examination.

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Letter 2

Sir

We enjoyed reading the article by Mercer *et al.* but disagree with the main conclusion of the paper that preoperative duplex scanning is required before all operations for primary varicose veins. Unfortunately, many hospitals do not have the non-invasive facilities to perform routine duplex scanning on all patients. We have adopted a policy of selective scanning for all patients with short saphenous vein reflux to identify the saphenopopliteal junction accurately, and for all patients in whom the veins cannot be controlled either by digital pressure over the saphenofemoral junction or a high thigh tourniquet. It has been well demonstrated that recurrence following high saphenous vein ligation is reduced by stripping of the long saphenous vein and we have adopted this practice routinely[1]. This obviates the requirement for duplex scanning of the long saphenous vein in the thigh in such patients. The only hard evidence that can be accepted for routine use of duplex in all patients is a reduction in the long-term recurrence rate following surgery. Unfortunately, there is no evidence that this is the case. There is a need for a prospective randomized controlled trial to establish the difference between a pragmatic approach such as ours and the counsel of perfection as detailed in their article.

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Letter 3

Sir

We read with interest the paper by Mercer *et al.* Although the saphenofemoral junction has a fairly consistent landmark the saphenopopliteal junction has variable anatomy and we are not told clearly how it was located by the authors. We have found tracing the short saphenous vein upwards to be useful for this. Why was the radiologist not blinded to the hand-held Doppler (HHD) results? How long a waiting time was there between assessment in clinic and duplex scanning? Sarin *et al.*[1] have shown that new sites of reflux may appear while patients are awaiting operation.

We too had a policy of duplex scanning for all patients with varicose veins but recently have had to use this service selectively as the waiting time for scanning became too long (approximately 1 year). This selective policy is supported in the paper by Kent and Weston[2], interestingly from the same institute as Mercer *et al.* Using the figures provided in the paper a negative predictive value of 0·91 is obtained for the saphenopopliteal junction. This value is similar to 0·96 in Kent and Weston's paper and suggests that duplex scanning is not needed in patients where HHD fails to show reflux in the popliteal fossa. Reflux in the popliteal fossa shown by HHD may arise from the popliteal vein, the saphenopopliteal junction or from gastrocnemius veins and should be verified by duplex.

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Letter 4

Sir

We read with interest the paper by Mercer *et al.* which concluded that duplex imaging is required before all operations for primary varicose veins. HHD was not accurate enough to plan surgery in their series. Undoubtedly, duplex scanning is more sensitive and specific than HHD for detecting sites of reflux in patients with varicose veins[1,2], but in our opinion this alone does not justify the routine use of duplex in these patients.

In their study, as in other series[1,2], the surgeons performing the clinical examination and HHD tests had to establish a diagnosis in every patient, even when their findings were doubtful or inconclusive. The option of 'site of reflux unknown, duplex required' was unavailable when in daily surgical practice these patients would be referred for additional duplex scanning. It would be interesting to know what the accuracy of HHD was in patients in whom there was little doubt about the clinical diagnosis.

In patients referred for duplex scanning because of inconclusive findings at clinical examination and HHD, the clinical impression agrees in only 39 per cent with the duplex findings[3]. On the other hand, when the surgeon feels comfortable with a clinical diagnosis, sensitivity and specificity of the clinical examination alone are high, especially for long saphenous vein reflux (98 and 89 per cent respectively)[4]. In a series of selected patients with primary (no previous surgery) and uncomplicated (no significant skin change) varicose veins, HHD is very accurate, both at the saphenofemoral junction (sensitivity 95 per cent, specificity 100 per cent) and the saphenopopliteal junction (sensitivity 98 per cent, specificity 95 per cent)[5].

With duplex scanning the treatment becomes more expensive, the examinations are time-consuming and, for surgeons seeing large numbers of varicose veins, the logistic implications of routine scanning are impractical.

In our opinion, therefore, duplex scanning can only be used routinely if it has been demonstrated to reduce recurrence in a randomized trial and to be cost-effective. We now reserve duplex scanning for selected patients with suspected saphenopopliteal reflux, recurrent varicose veins, a history of deep vein thrombosis or signs of chronic venous insufficiency, and when clinical examination and HHD are inconclusive, as in patients with obese legs[6].

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Letter 5

Sir

I read with interest the article by Mercer *et al.* in which they concluded that HHD ultrasonography is not sufficiently accurate to direct varicose vein surgery. In our yet unpublished series of 221 patients and over 300 limbs we came to the same conclusion. Many patients considered to have superficial vein insufficiency proved to have concomitant deep venous insufficiency which could cause recurrence of varicose veins. I wonder whether the authors have looked for the same finding?

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Authors' reply

Sir

We would like to thank all corresponding authors for the interest shown in our paper. Policies of selective duplex scanning depend on accurate assessment of long saphenous vein (LSV) reflux, high sensitivity for saphenopopliteal junction (SPJ) reflux and successful eradication of LSV reflux by stripping to the knee. Although our conclusions differ from those of other authors, our results are similar in terms of accuracy of examination by a consultant vascular surgeon with the exception of the series by Darke et al.[1].

Selective scanning of patients with suspected SPJ reflux allows accurate duplex localization of the junction which, in turn, allows immediate surgical access without extensive dissection. In terms of accuracy it excludes false positives from surgery but does not reduce the risk of inadequate surgery as patients with undetected SPJ incompetence will go undetected.

We agree with Meyer *et al.* that successful stripping of the LSV negates the requirement for detection and localization of perforators and this is also our routine surgical practice. Our experience, however, is that precise anatomical information is of value when percutaneous invagination (PIN) or the flexible stripper cannot be passed to the level of the knee or stripping is incomplete and local exploration of a known premarked perforator can be undertaken.

A delay between clinical assessment and duplex scanning may be a factor in developing new sites of reflux, as suggested by Khaira *et al.*, as the scans were performed on a waiting list for investigation of approximately 6 months. However, other studies, including that by Kent and Weston[2], have demonstrated some inaccuracy in HHD assessment compared with 'same-day' duplex scanning.

Surgery for primary varicose veins should aim to correct superficial venous incompetence and remove the presenting varicosities, thus minimizing the risk of recurrence. As suggested by several of the correspondents it would be interesting to assess the impact of selective and general duplex scanning policies on recurrence rates and the cost benefits of reduced requirement for revision surgery. It has, however, previously been demonstrated that inadequate surgery at a site of incompetence may be responsible for recurrence[3]. It would therefore seem reasonable that no surgery at a site of incompetence might have the same effect.

Duplex scanning is non-invasive, more accurate than HHD alone and offers information above and beyond, the readily quantifiable, accuracy of detection. In an ideal world, therefore, we believe that universal duplex imaging should be utilized in the investigation of complicated and uncomplicated primary and recurrent varicose veins.

The original title of this paper was 'Is preoperative duplex scanning required in all cases of primary varicose veins?' and the omission of the question was an editorial request. It is gratifying that our paper has prompted good debate and may contribute to interest in evaluation in a randomized trial. Until such time, resource limitations and logistics may well require a selective duplex scanning policy as discussed in the paper.

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Antireflux surgery in the laparoscopic era

Sir

I enjoyed the review of antireflux surgery (*Br J Surg* 1998; **85:** 1173–84) but take issue as to whether the results of randomized studies of open Nissen *versus* partial fundoplication procedures can necessarily be extrapolated to the laparoscopic era. Nissen fundoplication appears to be associated with a higher incidence of mechanical complications when performed laparoscopically[1], with an incidence of troublesome dysphagia up to 15 per cent at 1 year and a reoperation rate of 1–3 per cent[2,3]. No reoperation for this complication has been reported in six series of laparoscopic partial fundoplication[4]. The different pathophysiological features of differing fundoplication procedures may vary in their sensitivity to the altered geometry inherent in laparoscopic fundoplication.

Nissen fundoplication, even when short and floppy, results in a supracompetent cardia, with impairment of lower oesophageal sphincter (LOS) relaxation and virtual abolition of gas reflux and associated physiological acid reflux[5]. In contrast, the 'physiological' anterior fundoplication maintains physiological LOS relaxation and physiological acid exposure in the majority of patients, whether performed openly or laparoscopically[6,7]. These factors and the absence of anterior displacement of the oesophagus (which occurs in Nissen and posterior partial fundoplication) are likely to be relevant to the extremely low incidence of dysphagia and zero incidence of inability to belch and vomit reported by others[6–9].

It is indeed appropriate to subject anterior partial fundoplication in the laparoscopic era to the same degree of scrutiny as posterior partial fundoplication was in the open era. Independent assessment must confirm durability of reflux control by pH monitoring to be similar at 5 years to that reported following Nissen fundoplication[10]. Prospective randomized studies comparing laparoscopic anterior with floppy Nissen and posterior partial fundoplication are providing encouraging preliminary results[11]. Such trials will identify the procedure which confers greatest patient satisfaction with effective and durable reflux control and relative freedom from mechanical complications.

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In vivo pressure profiles of thigh-length graduated compression stockings

Sir

We read with interest the article by Wildin *et al.* (*Br J Surg* 1998; **85**: 1228–31). Compression stockings may work by increasing femoral vein blood flow velocity[1], but the surface pressure gradient is not necessarily strictly graduated as stated in the study by Wildin *et al.* as well as others[2,3]. As part of a study into the mechanism of action of compression therapy we investigated temperature changes and compression associated with the application of antiembolism stockings.

Temperature sensors were placed at the level of greatest prominence of the calf muscle on the medial aspect of both legs on six healthy volunteers. Skin surface temperature was monitored for at least 5 min before and after application of an appropriately sized stocking to the right leg. Compression was measured in four volunteers, 10 cm above the right medial malleolus, with the stocking applied four times. Median pressure when standing was 16 (range 6–25) mmHg. In all cases 5 min after application of the stocking the skin surface temperature had increased by a median of 0·5 (range 0 3–0·6) °C. On the leg without stocking, the median change was 0·0 (range −0·1–0 6) °C.

The variations in applied compression may imply that the mode of action of stockings is not solely related to the degree of compression. The applied compression may help, in part, by augmenting the calf muscle pump. The increase in skin surface temperature associated with application of compression stockings may suggest a temperature related effect on skin blood flow which may affect leg haemodynamics.

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3 Sparrow RA, Hardy JG, Fentem PH. Effect of 'antiembolism' compression hosiery on leg blood volume. *Br J Surg* 1995; **82:** 53–9.

Textbook of Anal Diseases

S L. Jensen and O V Nielsen (eds).
255 × 175 mm Pp 171 Illustrated 1998
Chur Harwood Academic Publishers £53

Essentially this book was written for doctors in training, but it might also be very useful for those who are not totally familiar with anal diseases. It focuses on symptomatology, and diagnosis and treatment of the most frequent disorders of the anus. It also covers some useful topics, such as anaesthesia, ambulatory surgery, complications and anal pharmacology. The two experienced authors have combined to cover the fields in a very practical manner. The chapters are fairly short, easy to read and provide the reader with much precise information, above all on the different methods of treatment. This will be an invaluable reference source both for those with an established interest in anal diseases and for those dealing with them for the first time. Clear and practical indications are given for the management of frequent problems. The work is scholarly and simply but well written. A bibliography is added to each chapter so that further reading is easy to select. It is really a book to be read by trainee, trainer, surgeon and casualty doctor.

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Vascular Brachytherapy. 2nd ed.

R. Waksman (ed)
260 × 180 mm Pp. 630 Illustrated 1998
Armonk, New York Futura Publishing Company US $149

This is a book for the vascular specialist with an interest in this experimental therapy. Brachytherapy refers to the delivery of either γ or β radiation to the inside of a vessel after a vascular intervention (usually angioplasty or stenting) to prevent the proliferative component of restenosis which is the major cause of failure of these treatments. There is also a discussion on external beam radiotherapy, which is a related subject. As the foreword wisely remarks, this work is the product of a honeymoon phase of clinical research, mostly driven by industry. There are clearly many reasons for industrial interest, not least the amount of equipment and specialized materials that are required for this form of treatment. A suitably cautionary note is sounded throughout the book, 'we will have to deal with difficulties once the honeymoon is over'.

Many vascular clinicians will have severe doubts about the appropriateness of radiotherapy in these circumstances bearing in mind the severe long-term vascular damage inflicted by external beam radiotherapy for malignant disease. No author in this book denies that such a possibility exists and that radiation treatment for restenosis may prove to be the proverbial sledgehammer to crack a nut. However, there are reasons for believing that the radiation dose is not as great as that inflicted by treatments for malignant disease and that long-term damage may not be as severe. Whether it is appropriate or ethical to confirm these beliefs in experimental human treatments is not discussed in this book. The subject is rapidly changing, as evidenced by the appearance of a second edition of the book even before most people knew that there was a first. There is a number of clinical trials described which are all very preliminary, using small numbers. The sole double-blind trial randomized only 55 patients. Most of the trials are focused upon feasibility and safety of the equipment involved, including issues such as radiation shielding and dosimetry. In as far as this book draws together many disparate strands from a rapidly evolving experimental therapy, it is a useful freeze-frame of a rapidly evolving subject; but, even as this review appears, I am sure that many of its statements are already out of date.

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Liver Cancer (part of the M.D. Anderson Solid Tumour Oncology Series)

S. A Curley (ed). R. E. Pollok (series ed.).
240 × 157 mm Pp 253 Illustrated 1998
New York, New York Springer £68 50

I enjoyed reading this review of the management of liver cancer. It is concise, logically set out, easily readable and very well referenced. The subject, I believe, is of great topical interest and, in contrast to other tomes on this subject, it is almost totally clinically orientated as opposed to pathology orientated. This is a rapidly changing area which is well discussed and well presented at this time. The chapter on the treatment of cholangiocarcinoma is typical of others, starting with a paragraph on epidemiology leading into a discussion of various classification systems, followed by diagnostic techniques of differing specificities leading to careful evaluation of the various treatment options available. The chapter is then finished with a concise and relevant conclusion. My only slight criticism is that, in my view, the chapter on cryosurgery is very detailed and possibly overlong; it is given an importance out of proportion to its effectiveness in treating liver cancer. The book is rounded off by two stimulating chapters on the biology of colorectal cancer liver metastasis and gene therapy for hepatocellular carcinoma, both of which are typically well written and well referenced. I believe this book would be an asset to all individuals and departments engaged in the management of liver cancer.

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Scientific Surgery

The British Journal of Surgery is committed to practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English language publications. A collection of all these papers will be available in the Scientific Surgery Archive which will be held on *The British Journal of Surgery* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Randomized trials

Rosen M, Chan L, Beart Jr RW, Vukasin P, Anthone G. Follow-up of colorectal cancer: a meta-analysis. *Dis Colon Rectum* 1998; **41:** 1116–26.

Five randomized studies including 2005 patients were evaluated Cumulative survival at 5 years was 1 16 times higher in intensively followed patients (*P* = 0 003)

Ingram M, Wright TA, Ingoldby CJH. A prospective randomized study of calcium alginate (sorbsan) *versus* standard gauze packing following haemorrhoidectomy. *J R Coll Surg Edinb* 1998; **43:** 308–9.

In this study of 50 patients, sorbsan significantly reduced pain at the time of pack removal and first bowel action, but did not reduce overall analgesic requirements

Walker SR. A randomized controlled trial comparing 21-G needle with a 23-G needle for fine-needle aspiration of breast lumps. *J R Coll Surg Edinb* 1998; **43:** 322–3.

There was no significant difference in cytological yield between the needles in a comparison of 125 breast aspirations

Cochrane RA, Edwards AT, Crosby DL, Roberts CJ, Lewis PA, McGee S *et al.* Senior surgeons and radiologists should assess emergency patients on presentation: a prospective randomized controlled trial. *J R Coll Surg Edinb* 1998; **43:** 324–7.

Ninety-five patients with acute abdominal pain were assigned to immediate ultrasonographic assessment by a senior radiologist or conventional management The intervention significantly reduced the need for admission as judged by a senior surgeon from 90 to 70 per cent without compromising outcome

Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R *et al.* Randomised trial of irinotecan *versus* fluorouracil by continuous infusion after fluorouracil fails in patients with metastatic colorectal cancer. *Lancet* 1998, **352:** 1407–12.

In this study of 267 patients, irinotecan improved median survival from 8 5 to 10 8 months without adversely affecting quality of life

Cunningham D, Pyrhonen S, James RD, Punt CJA, Hickish TF, Heikkila R *et al.* Randomised trial of irinotecan plus supportive care *versus* supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998; **352:** 1413–18.

Some 279 patients were included, survival at 1 year was significantly better with irinotecan (36 2 *versus* 13 8 per cent) and quality of life was improved

Pedrazzoli S, Dicarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C *et al* Standard *versus* extended lymphadenectomy associated with pancreaticoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas. *Ann Surg* 1998; **228:** 508–17.

Extended lymphadenectomy did not increase morbidity and mortality rates in this study of 81 patients Overall survival was similar but extended surgery improved the survival rate in patients with involved lymph nodes

The UK Small Aneurysm Trial participants. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. *Lancet* 1998; **352:** 1649–55.

Some 1090 patients with aneurysms from 4 0 to 5 5 cm in diameter were followed for 5 years Mortality rates at 6 years were similar, there was no advantage for early surgery.

The UK Small Aneurysm Trial participants. Health service costs and quality of life for early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. *Lancet* 1998; **352:** 1656–60.

Some 1090 patients with aneurysms from 4 0 to 5 5 cm in diameter were followed for 5 years The cost of early surgery was greater than that for surveillance, though surgery was associated with improvements in some features of health-related quality of life

***The British Journal of Surgery* website can be found at *www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.**

Instructions to authors

The British Journal of Surgery publishes original articles, reviews and leading articles all of which are submitted to peer review.

An article is reviewed for publication assuming that its contents have not been submitted simultaneously to another journal, have not been accepted for publication elsewhere and have not already been published. **Any attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** Please submit with your manuscript copies of any other papers (published, in press, or submitted for consideration elsewhere) that relate to the same subject. It is essential that you submit any other publications or submissions that use the same data set to allow assessment of any potential overlap Indicate on the title page whether the paper is based on a previous communication to a society or meeting. Articles and their illustrations become the property of the Journal unless rights are reserved before publication.

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Disks

Following final approval of articles you must submit the accepted version on disk IBM-compatible disks would be preferred An accurate hard copy must accompany each disk, together with details of the type of computer used, software and disk system. **Do not justify.** Please send us digital versions of your figures. Ideally these should be sent in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Disks will not be returned to authors.

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Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which facilitates resubmission of papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* (*N Engl J Med* 1997; **336**: 309–15), or obtain 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £2 95 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs you must state in parentheses the brief name and address of the manufacturer** Generic names should normally be used

Original articles

Original articles should normally be in the format of introduction, patients and methods, results and discussion Please provide a 200-word structured abstract. Lengthy manuscripts will be returned for shortening. The discussion in particular should be clear and concise and limited to matters arising directly from the results. Avoid discursive speculation. **Randomized clinical trials** should be clearly identified as such in the title and abstract.

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors are advised to contact Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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The Editors commission leading articles that are 600-900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication

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Manuscripts must be clearly reproduced with adequate space for editorial notes Present the text on one side of sheets of A4 paper (210 × 297 mm) with double spacing and 4-cm margins. **Begin each section (abstract, introduction, patients and methods, results and discussion) on a new page. Manuscripts that do not conform to these requirements will be returned for recasting.**

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On the title page give (1) the title of the article; (2) the name and initials of each author, (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone, facsimile and email numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review, etc).

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Use abbreviations *sparingly* Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension. Abbreviations must be used consistently and must be defined on first use.

Numbers and units

Use the decimal point, not a comma, for example 5·7. Use a space and not a comma after thousands and multiples thereof, for example 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg).

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For detailed guidance on the handling of statistical material consult *Br J Surg* 1991, **78**: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results

Design

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Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

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References

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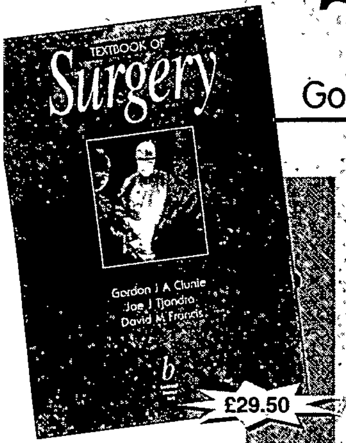

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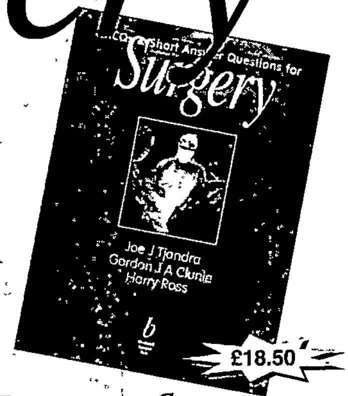

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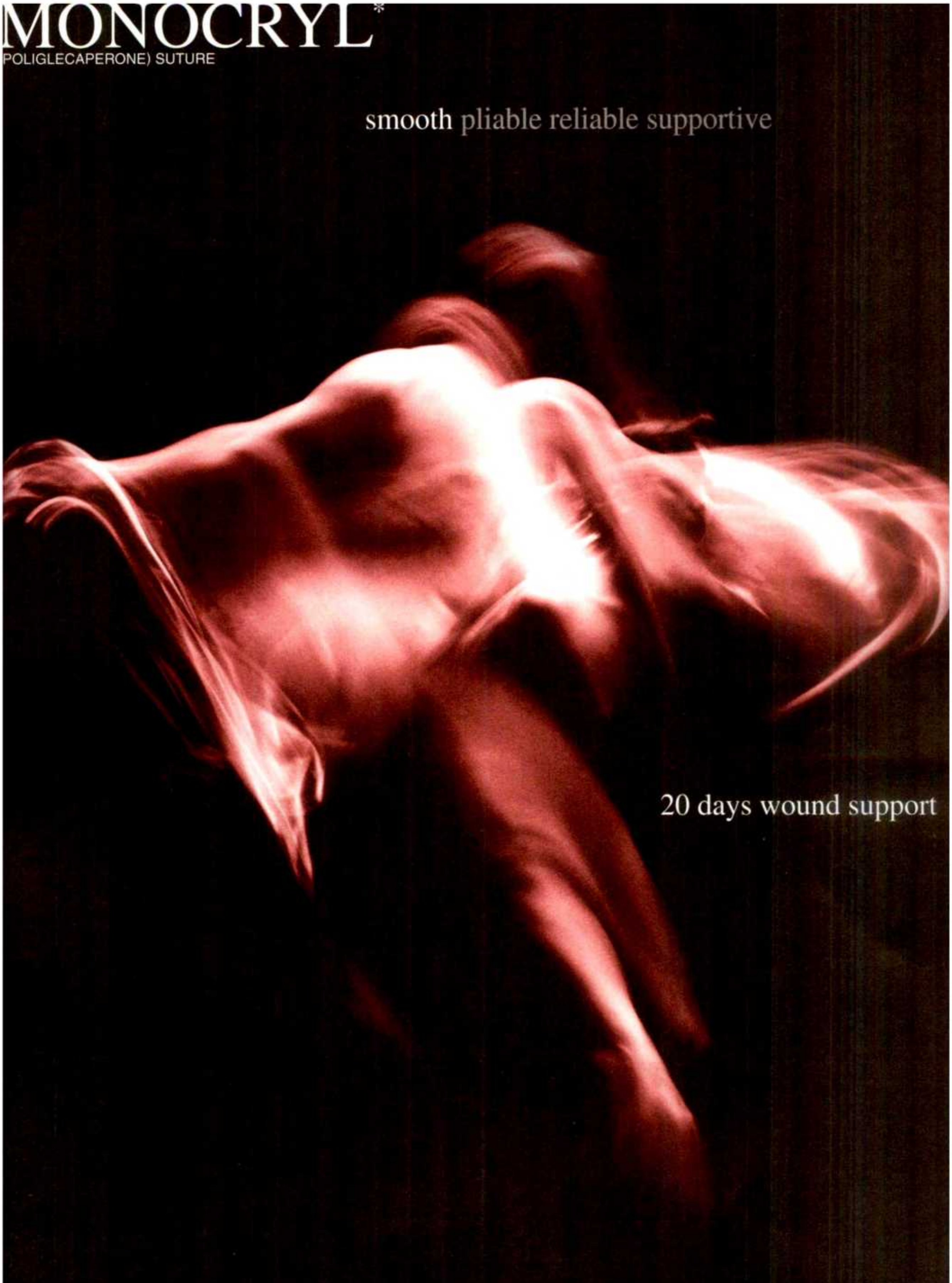

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Inguinal hernia repair

S. Nicholson

York District Hospital, Wigginton Road, York YO3 7HE, UK

Over a century has passed since the landmark series of inguinal hernia repairs carried out by Eduardo Bassini[1]. Had his early publications been in the English language much of the controversy that has existed over the past 100 years might have been avoided. Bassini realized that the key to the normal inguinal canal was the integrity of the posterior wall and, in particular, the transversalis fascia. He devised an operation in which the transversalis fascia was divided and repaired using interrupted sutures, thereby reconstructing not only the deep inguinal ring but also the posterior wall of the inguinal canal, a procedure applicable equally to indirect and direct hernias.

Bassini's operation was largely ignored or misinterpreted during the first half of the 20th century. Many different methods were devised but results were generally poor because they failed to correct the primary defect in the deepest layer of the posterior wall. Although good results were reported by dedicated technicians, those of the general surgical community were much less satisfactory. Bassini's essential concept was rediscovered just after World War II by a surgeon working in Toronto, Canada. In 1953 Earle Shouldice[2] reported a series of 8317 hernia repairs with an overall recurrence rate to 10 years of 0·8 per cent; this marked the start of the modern era of hernia surgery.

The Shouldice method has consistently provided excellent results in the hands of dedicated hernia surgeons[3]. The technique employs a four-layer overlapping repair of the posterior wall of the inguinal canal. Although it is not an entirely tension-free repair, such tension as there is is distributed between multiple anchorage points along the suture lines which produces very little strain at any one site; this undoubtedly contributes to a very low failure rate. The technique is applicable equally across the whole spectrum of inguinal hernia pathology, including and especially sliding hernias. One slight drawback is that surgeons in training may find the method difficult to master and so produce poorer results than their senior colleagues[4], but a modification to the classical Shouldice technique, as described by Berliner, greatly simplifies the operation and facilitates both teaching and learning. Excellent results have been obtained using the two-layer Berliner procedure in the UK but there is still some evidence that a poorer outcome is obtained by trainees[5].

The past 5 years have seen an impressive rise in the popularity of the tension-free mesh repair, originally popularized by Lichtenstein and Shulman. This operation is simple to perform and gives excellent early results with low complication rates and an early return to full activity[6]. Surgeons in training find the technique easier to master than the two-layer or conventional four-layer Shouldice technique, but there are as yet relatively few long-term data on the use of the method in non-specialist centres and the outcomes being obtained by surgeons in training.

Good early results have also been obtained with laparoscopic techniques; transabdominal preperitoneal repair is probably the most widely used. Operating times and theatre costs are consistently higher with this type of surgery; overall pain scores and complication rates differ little from those of open operation[7]. Any small advantage in early return to physical activity is likely to be outweighed by cultural attitudes, which still prevail in primary care medicine, against early return to work following hernia surgery, and the fact that up to half the patients treated are already of retirement age. It seems unlikely therefore that laparoscopic hernia repair will replace open techniques in the treatment of primary inguinal hernia. Laparoscopic techniques may have a place in expert hands in the management of selected patients with recurrent hernia; in practical terms they offer little real advantage over conventional preperitoneal mesh reinforcement[8].

A recent large review[9] has concluded that, of the open techniques, the Shouldice type of repair and the tension-free mesh repair give the most consistent good results. It also concluded that local anaesthesia was as safe and acceptable as general or regional anaesthesia, and that for most patients day-case surgery was as appropriate as planned overnight stay.

With over 80 000 groin hernia operations carried out in the UK alone each year, and a deepening crisis in surgical manpower resulting from increased surgical subspecialization and greater public and political demands for quality in surgical practice, inguinal hernia repair will remain for the foreseeable future a procedure likely to be delegated to non-consultant staff. It is essential, therefore, that we design safe and simple pathways for managing these patients. While useful guidelines exist[10], there is as yet relatively little evidence of best practice being implemented across Britain's National Health Service.

Training of surgeons in the techniques of hernia repair remains haphazard with the trainee often adopting uncritically the method demonstrated by his or her consultant on a handful of occasions. It is hardly surprising that the generality of results compares so unfavourably with those obtained in specialist centres; at the Shouldice Clinic, new staff surgeons are highly supervised for their first 1000 operations. Current evidence suggests that trainees should be instructed in only two techniques, the two-layer (or four-layer) Shouldice type operation and the tension-free mesh repair. Laparoscopic hernia repair should remain an operation for those with an interest and expertise in advanced laparoscopic surgery. Management of the difficult inguinoscrotal, recurrent hernia should be the remit of surgeons who have developed a particular interest in this field. The care of patients with recurrent hernia, in particular, needs to be refined; a fourth or fifth recurrence should be a thing of the past.

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Applications should be sent to Mr J. R. C. Sainsbury, Company Secretary, The British Journal of Surgery Society, Department of Surgery, The Royal Infirmary, Lindley, Huddersfield HD3 3EA, UK by 31 May 1999.

J. R. C. Sainsbury

Obscure lower gastrointestinal tract bleeding

Lower gastrointestinal bleeding may sometimes be profuse and the site of haemorrhage may be difficult to find. What should one do when faced with such a situation? Mr M. G. Thomas of the Bristol Royal Infirmary suggests a systematic approach.

In most patients the cause of an acute significant colonic bleed is easy to determine; in some, however, it is not. The term 'obscure bleeding' may be used to describe three clinical situations: (1) a common cause exists but it has been difficult to diagnose or it has been overlooked; (2) bleeding results from multisystem disease; and (3) multiple investigations have failed to localize the site of haemorrhage[1]. In most patients even profound acute lower gastrointestinal (GI) haemorrhage is self-limiting, allowing investigations to be performed both during the acute episode and between bleeds. A detailed history, clinical examination and haematological investigations are mandatory. It is important to question personal and technical diagnostic accuracy, with a willingness to repeat investigations such as upper and lower GI endoscopy. Those with recurrent lower GI tract bleeding that is difficult to diagnose should undergo a sequence of investigations ranging from pan-endoscopy, through small and large bowel radiological contrast studies, radioisotope scan, echocardiography (to detect aortic stenosis) and selective visceral angiography, to peroperative enteroscopy. This sequence should help identify the site or sites of bleeding before embarking on surgery; if an operation is carried out, it should be as the final diagnostic and therapeutic step[2]. In some situations it may be wise to consider a separate semielective bowel resection after diagnostic laparotomy to allow the patient to have sufficient counselling (e.g. a patient with rectal arteriovenous malformation).

Endoscopy should be used before surgery to help localize the site of bleeding to allow limited resection, embolization or endoluminal therapy; colonoscopy is the most convenient and effective first procedure[3]. Very occasionally colonoscopy can localize a bleeding point during an acute episode but, in the majority of patients, the view is poor and elective or interval diagnostic colonoscopy is undertaken. If an arteriovenous cause of the bleeding is found, argon beam ablation, electrocautery, laser ablation or injection sclerotherapy may be used to stop the acute haemorrhage. Patients with widespread colonic angiodysplasia may require multiple procedures. Argon beam ablation is particularly useful in the elderly patient with widespread colorectal mucosal angiodysplasia (e.g. congenital von Willebrand's disease). Colonic arteriovenous malformations frequently coexist with small bowel disease and so it is prudent also to perform upper GI endoscopy and peroperative enteroscopy[1,4].

Many vascular anomalies may cause lower GI tract bleeding and several of these are related to multisystem disease (e.g. Klippel–Trenaunay syndrome, hereditary telangiectasia and some cases of Dieulafoy's vascular malformation). Qualitative and quantitative changes in mucosal vasculature occur in both hepatic cirrhosis and portal hypertension, and these can usually be treated by a combination of injection sclerotherapy and octreotide[5]. Angiodysplasia is a progressive venular dilatation leading to incompetence of the precapillary sphincters, thereby producing arteriovenous malformations. It is found in association with cardiovascular disease, peripheral vascular disease and aortic stenosis. The well recognized association between aortic stenosis and angiodysplasia might be explained by an acquired reversible deficiency of large multimers of von Willebrand factor[6], and replacement of the stenotic valve has been reported to stop gastrointestinal bleeding in over 90 per cent of patients[7]. Angiodysplasia of the right colon frequently occurs with coexisting jejunal or ileal malformations. If surgery is contemplated, all lesions detected should be excised to reduce the need for further operations[1,4]. Approximately 20 per cent of patients undergoing surgery for angiodysplasia will rebleed and excision should be regarded as a therapeutic but not a curative measure.

Selective visceral angiography and radioisotope scanning may be viewed as complementary investigations in the preoperative localization of a bleeding site[8]. ^{99m}Tc-radiolabelled red blood cell scanning has a high predictive value when positive or negative in cases of lower GI tract haemorrhage. The long intravascular half-life of labelled red cells allows repeat scanning and increases the probability of isolating those lesions that bleed intermittently. ^{99m}Tc-radiolabelled sulphur colloid and ^{99m}Tc-labelled diethylenetriamine penta-acetate have short intravascular half-lives and so the patient needs to be bleeding actively at the time of the investigation to ensure success. Selective visceral angiography can be very useful in localizing the site of bleeding during an acute episode and an increasing number of patients may be suitable for highly selective mesenteric vessel embolization[9]. It is essential to observe patients closely following colonic embolization to detect signs of large bowel ischaemia. In most cases colonic ischaemia following superselective embolization is self-limiting, but progressive symptoms should prompt surgical intervention. The preoperative localization of bleeding by either isotope scan or angiography may facilitate minimal access surgery (e.g. laparoscopically assisted colectomy or Meckel's diverticulectomy). In patients presenting with recurrent, acute, profuse bleeding, angiography performed early in the episode may also prove useful. Patients should be advised to come direct to hospital as soon as recurrent bleeding starts (this is often proceeded by generalized abdominal discomfort) as this allows urgent angiography to help localize the bleeding site and aids the planning of definitive treatment.

Those who are actively bleeding from the large bowel in whom multiple attempts at preoperative localization have failed may require surgery. At laparotomy a colonoscope may be passed both through the mouth and anally to perform pan-endoscopy, with the surgeon and the assistant guiding the scope. During peroperative enteroscopy the operating and theatre lights are dimmed to allow transillumination of the bowel and intraluminal inspection. Traumatic lesions may be difficult to differentiate from small ulcers or arteriovenous malformations and so inspection during scope insertion is more useful than during withdrawal. The surgeon should mark the site of any mucosal abnormality with a serosal suture. In patients with profuse colorectal bleeding the view during peranal colonoscopy is often obscured by blood. A terminal ileal enterotomy allows retrograde small bowel enteroscopy and prograde lavage of the colon. After placing a soft bowel clamp on the ileum a large-bore Foley catheter is passed through the ileocaecal valve and the balloon is inflated. Colonic lavage is performed using 6 l of warmed saline. An excellent examination of the entire colon and rectum can be achieved after advancement of the colonoscope through the ileocaecal valve or via a caecostomy.

In summary, preoperative localization of a bleeding site should be the aim in all patients with significant lower GI bleeding. In those rare circumstances when multiple attempts at localization have failed, peroperative endoscopy can be useful in identifying a bleeding point.

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Endoleak after stent-graft treatment of abdominal aortic aneurysm: a meta-analysis of clinical studies

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Background: Endoleak is the major complication after endovascular treatment of abdominal aortic aneurysm (AAA) and its incidence seems to remain significant. Little is known about the association of device type and configuration with respect to the incidence, location, time of onset and fate of endoleakage.

Methods: A meta-analysis was performed via a Medline search of clinical studies after 1995 dealing with the endovascular treatment of AAA. Details of number of patients treated, configuration and type of endovascular device were collected. Data concerning site of origin, time of occurrence and fate of the endoleak were retrieved, along with information on change in diameter of the aneurysm with time.

Results: The 23 publications included reported on 1189 patients. The 1118 patients with successfully inserted transfemoral endovascular grafts experienced 270 endoleaks (24 per cent). The majority arose from the distal stent attachment site (36 per cent), were present immediately after stent-graft placement (66 per cent) and were persistent in time (37 per cent). Tube grafts were more frequently affected by endoleakage (35 per cent; $P < 0.0001$), especially at the distal stent attachment site (51 per cent), than bifurcated grafts (18 per cent; $P = 0.004$) and aortounilateral devices (20 per cent; $P = 0.70$). Self-expandable stent-grafts were more frequently associated with endoleaks (25 per cent) than balloon-expandable stent-grafts (17 per cent) ($P = 0.037$).

Conclusion: Endovascular treatment of AAA is an evolving field. Even after the initial learning curve and attention to device-related problems, it is still accompanied by a significant number of endoleaks. Uniform presentation of results of treatment is necessary for analysing the effect of differences between patients, aneurysm morphology and device type.

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Introduction

Endoleak is a major complication after the endovascular treatment of abdominal aortic aneurysm (AAA). It implies failure to exclude the aneurysm, an insufficient treatment which carries a risk of aneurysm growth and, eventually, rupture.

AAA morphology is an important factor in the appearance of endoleak, and many authors have also attributed a high level of endoleakage to a steep learning curve and the development problems associated with endovascular devices. However, even after the initial learning and development period, the rate of endoleakage remains substantial.

Little is known about the effect of device type and configuration on the incidence, location, time of onset and fate of endoleakage. The present study aimed to evaluate whether or not the number of endoleaks has decreased during and after the learning period, and after the replacement of several 'first-generation' endovascular devices; a meta-analysis was made of the clinical studies published so far. A further analysis of several variables (stent-graft configuration, type of device, type of stent) was performed to relate them to site and time of endoleakage.

Materials and methods

A Medline search of English, German, French and Dutch language medical literature was made using the keywords: aorta, aortic, aneurysm, stent, endograft and endoprosthesis. The search was limited with the terms: human, not case report (*Table 1*). A total of 231 articles were selected. The abstract of each article was studied and, if there was any suggestion of a clinical series of treatment of AAA including short- or long-term follow-up, the full text was retrieved (44 papers). Articles were included if (1) they were published in 1995 or later and (2) they reported on the endovascular stent-graft treatment of at least ten AAAs.

Reports on patients whose data were also included in a subsequent article were excluded. Minor overlap was accepted and is reported where and when it occurs. In cases of considerable overlap of patient data, the publication with the greatest number of treated AAAs was included. Reports were also excluded if patients treated for an AAA could not be differentiated from those treated for aneurysm at other locations. Publications before 1995 were ignored because of a requirement for studies with 'considerable' experience in the endovascular treatment of AAA and a desire to exclude the initial learning curve of the pioneers who introduced the technique. The cut-off year of 1995 was chosen because before this date articles relevant to the search criteria are rare[1–3].

All articles were studied carefully for the following variables: number of patients treated, number and type of transfemorally placed endovascular grafts, length of follow-up and 'primary' (during initial treatment) conversion rate. The following variables were also recorded: site of origin (proximal or distal stent attachment site, through graft material or between parts of a modular system (graft related), occluder related, through an aneurysm side branch or hypogastric artery); time of appearance (immediate – detected before discharge after initial treatment, delayed – initially absent and occurring after discharge, recurrent – after 'spontaneous' seal or after initial successful interventional procedure); and fate of the endoleak (persistent, 'spontaneously sealed' – previously visible endoleak no longer detectable by imaging techniques, probably sealed by thrombosis, sealed by either radiological intervention or by 'secondary' conversion to open repair).

Table 1 Medline enquiry that formed the basis of the literature search for data for the meta-analysis

#1 Stent (*n* = 5226)
#2 Endograft or endograft- or endografting or endografts or endografts- (*n* = 72)
#3 Endoprostheses or endoprostheses- or endoprosthesis or endoprosthesis- (*n* = 1220)
#4 Aorta or aorta- or aortic or aortic- (*n* = 38 332)
#5 Aneurysm or aneurysm- (*n* = 14 829)
#6 'Human' in mesh heading
#7 'Case report' in mesh heading
#8 #1 or #2 or #3 (*n* = 6178)
#9 #4 or #5 (*n* = 37 453)
#10 #8 and #9 (*n* = 600)
#11 #10 and #6 (*n* = 521)
#12 #11, not #7 (*n* = 308)
#13 Published 1995 or thereafter (*n* = 242)
#14 Language: English, German, French or Dutch (*n* = 231)

Data were also collected about the relation between the diameter change of the aneurysmal sac and the presence or absence of endoleakage. If data could not be retrieved, they were considered as 'missing'.

Fisher's exact test was used to determine the statistical significance endoleak ratio between groups.

Results

Data retrieval

Ninety-seven per cent of the data about the site of origin of the endoleak was available in the publications. For the time of occurrence of the endoleak and for its fate with time, data retrieval was 95 and 98 per cent respectively. Information about the diameter of the aneurysm for the total group of patients treated by endovascular repair, specified for the subgroups with and without endoleakage, was presented in only two articles describing 53 stent-grafts (5 per cent)[4,5]. This information without specification for the subgroups was supplied in three articles containing 250 stent-grafts (14 per cent)[6–8]. In four papers the fate of the aneurysmal sac with time was described in cases of endoleakage (8 per cent of all stent-grafts)[4–7]. Specification of the total or mean follow-up period was available for 31 per cent of the stent-grafts.

All stent-grafts

A total of 23 of 231 publications met the criteria for inclusion and these were included in the analysis[4–26]. The 23 studies reported on 1189 patients with AAA who were treated with an endovascular stent-graft. Seventy-one procedures (6 per cent) were converted to laparotomy at the initial implantation (primary conversion), resulting in a total of 1118 patients with stent-grafts available for follow-up analysis. Of these patients, 270 (24 per cent) had an endoleak, either immediately after treatment or during follow-up. Weighted for the number of stent-grafts per publication, mean(s.d.) follow-up was 11(5) (range 0–60) months.

Site of origin, time of occurrence and the fate of all endoleaks are illustrated in *Fig. 1*. The majority (36 per cent) originated from the distal stent attachment site and were detected before discharge of the patient from hospital after initial treatment (66 per cent). Spontaneous

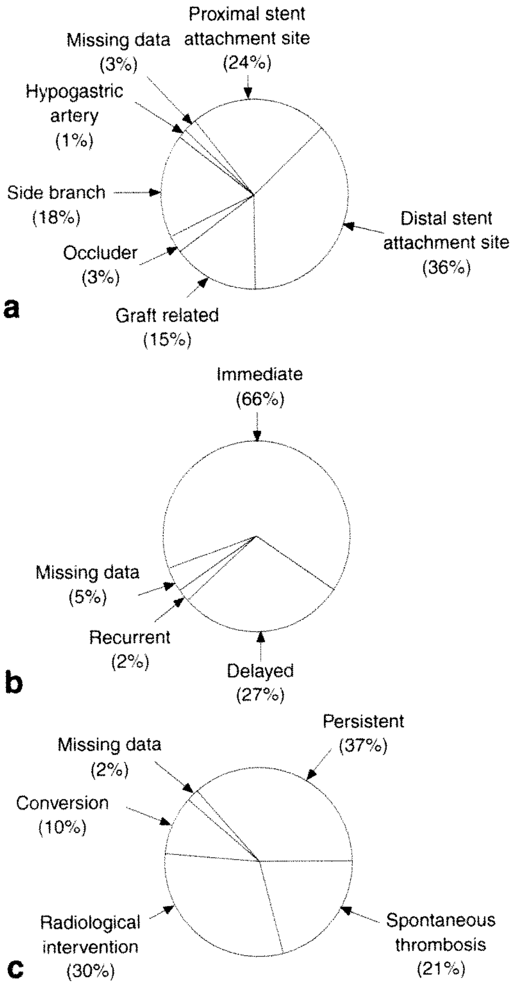

Fig. 1 Endoleaks ($n = 270$) for all stent-grafts ($n = 1118$) according to **a** site of origin, **b** time of occurrence and **c** fate of the endoleak with time

thrombosis occurred in 21 per cent of all endoleaks. The choice between a 'wait-and-see' policy or intervention, either radiologically or by conversion to open operation, varied widely between studies. In the eight studies with more than 15 endoleaks[8,10,15,16,20–22,24] the ratio of 'wait-and-see' to intervention varied from 12 : 1[24] to 1 : 10[10].

For the total stent-graft group with information on aneurysm diameter during follow-up (250), an increase in diameter was recorded in 15 per cent, stabilization in 35 per cent and a decrease in 50 per cent. If the diameter change is considered for the subgroup with endoleakage (75), the results for growth, stabilization and decrease are 86, 14 and 0 per cent; for the subgroup without endoleakage (46) the results are 0, 53 and 47 per cent.

Rupture of an aneurysm after endovascular treatment was reported six times in five papers[11,18,19,22,27]. These five publications contained 219 patients with stent-grafts and reported 65 endoleaks (30 per cent); the ruptured aneurysms after stent-graft therapy were therefore associated with 9 per cent of the endoleak group. However, for the total number of endoleaks (270) in the publications included, the overall rupture rate was 2 per cent.

In the first year of the Medline search (1996) the endoleak rate was 25 (16 per cent) of 155 stent-grafts; ten of these endoleaks were delayed in occurrence. Analysis of articles published in 1997 and 1998 revealed 985 patients with stent-grafts in 18 papers. They suffered 245 endoleaks (25 per cent), of which 63 (26 per cent) were detected during follow-up.

Stent-graft configuration

Numbers of patients, implanted stent-grafts and endoleaks for each stent-graft configuration are shown in *Table 2*.

Table 2 Studies separated according to device configuration

Type of stent-graft	No. of patients*	No. of stent-grafts	No. of endoleaks	*P*§
Tube[4,6,8,10,14,16,20,24,25]	244	226	78 (35)	< 0·0001
Bifurcated[8,10,12,14,16,18,26]	287	276	49 (18)	0·004
Aortounilateral†[5–7,17,24]	108	93	19 (20)	0·70
Mixed‡[9,11,13,15,19,21–23]	550	523	124 (24)	0·78
All studies	1189	1118	270 (24)	

Values in parentheses are percentages. *On an intention-to-treat basis. †Including contralateral occluder and femorofemoral crossover bypass. ‡Endoleak data in these studies could not be broken down into type of stent-graft. §*Versus* all other types (Fisher's exact test)

For those studies described as 'mixed', it was not possible to separate data according to device configuration. Tube grafts had a higher percentage of endoleaks (35 per cent), especially those originating from the distal stent attachment site (51 per cent), compared with the bifurcated stent-graft (18 per cent) and the aortounilateral device (20 per cent) (*Fig. 2*). The percentage of tube grafts with endoleaks was significantly higher than that of the bifurcated grafts ($P < 0·0001$) and the mixed group ($P = 0·002$). Unlike the other devices, the aortounilateral configuration did not result in any endoleakage originating at the distal stent attachment site.

Device type

Devices of various designs were used (*Table 3*). The proportion of endoleaks in the Corvita (Corvita Corporation, Miami, Florida, USA) group (52 per cent) and the

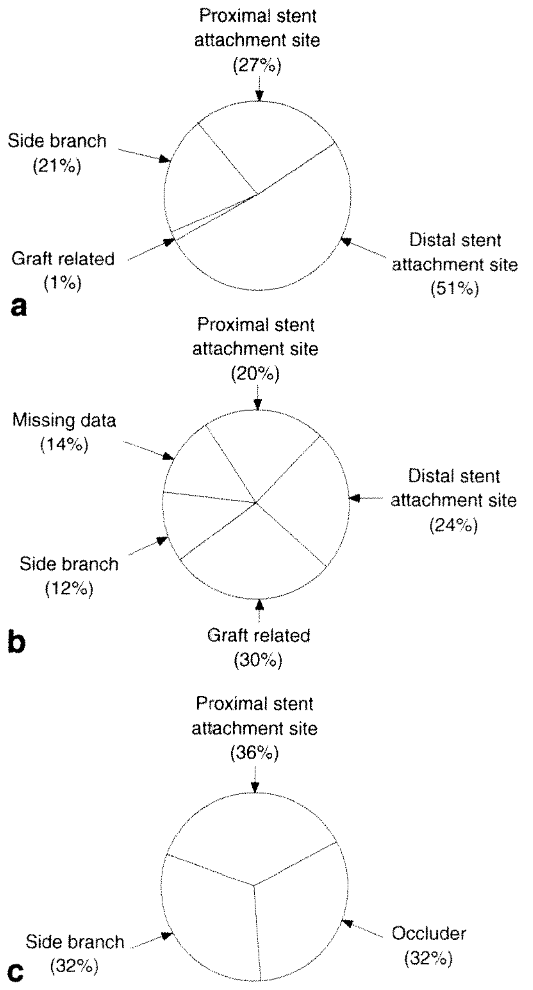

Fig. 2 Endoleaks, according to site of origin, associated with **a** tube grafts ($n = 226$; 35 per cent endoleaks), **b** bifurcated stent-grafts ($n = 276$; 18 per cent endoleaks) and **c** aortounilateral stent-grafts ($n = 93$; 20 per cent endoleaks)

first-generation EVT (Endovascular Technology, Menlo Park, California, USA) group (44 per cent) was higher than that of the other devices, which varied from 6 to 26 per cent. In the Stentor–Vanguard group (Stentor, Mintec, Freeport, The Bahamas; Vanguard, Boston Scientific Corporation, La Garenne-Colombes, France), 24 per cent of the endoleaks were 'graft related'. Endoleak originating from a space between parts of a modular system was only occasionally reported and generally originated from a defect in the graft material. With the Stentor device, this problem originated from the graft suture line and is now resolved by the replacement of this device by the Vanguard. Recently, cases of late development of fabric defect have been reported for the Vanguard device.

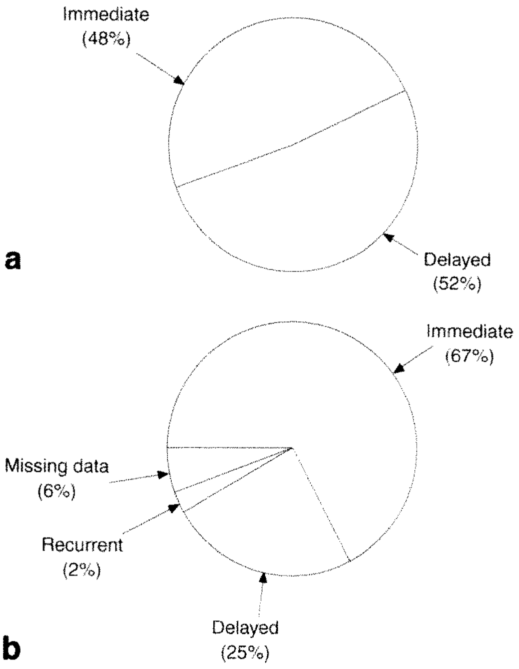

Fig. 3 Occurrence of endoleaks according to follow-up interval for **a** balloon-expandable stent-grafts and **b** self-expandable stent-grafts ($n = 889$ and $n = 166$)

Table 3 Studies separated according to device type

Type of stent-graft	No. of patients*	No. of stent-grafts	No. of endoleaks
AneuRx†[26]	16	16	1 (6)
Chuter[12]	57	54	8 (15)
Corvita[15]	31	31	16 (52)
EVT[4,11,20,24]	126	117	52 (44)
Ivancev–Malmö[5,17]	75	66	17 (26)
Parodi[6,7,9,22,24]	198	175	35 (20)
Perth‡[18]	21	21	4 (19)
Stentor/ Vanguard[8,10,13,14,19,21]	465	459	90 (20)
Talent§[8,23]	33	25	5 (20)
White–Yu GAD[25]	36	34	8 (24)
Mixed¶[16]	131	120	34 (28)
All studies	1189	1118	270 (24)

Values in parentheses are percentages. *On an intention-to-treat basis. †Medtronic, Cupertino, California, USA; ‡William A. Cook Australia, Brisbane, Australia; §World Medical, Sunrise, Florida, USA.¶Endoleak data in this study could not be broken down into type of device. GAD, graft attachment device

Balloon-expandable *versus* self-expandable stent-grafts

Many more self-expandable stent-grafts (889) of various types (Nitinol stents, Gianturco (William Cook Europe, Bjaeverskov, Denmark) and other stainless steel stents) could be analysed than balloon-expandable stent-grafts

(166). The overall endoleak rate was significantly higher for the former (25 per cent) than the latter (17 per cent) ($P = 0{\cdot}037$). The balloon-expandable stent-grafts had a higher proportion of distal endoleak (66 per cent) than the self-expandable grafts (34 per cent) ($P = 0{\cdot}001$); endoleaks in the tube graft group were predominantly responsible for this difference. Another difference between the devices was the proportion of delayed endoleaks. In the balloon-expandable stent-graft group, 52 per cent of the endoleaks were delayed while only 25 per cent were delayed in the self-expandable group (*Fig. 3*).

Discussion

In 1996, White *et al.*[28] introduced the term 'endoleak', to distinguish it from 'leak' (extravasation of blood into the peritoneal cavity or tissues surrounding the aorta, associated with aneurysm rupture). Endoleakage was defined as 'a condition associated with endoluminal vascular grafts, defined by persistence of blood flow outside the lumen of the endoluminal graft but within an aneurysm sac or adjacent vascular segment being treated by the graft'[29]. Later, the same authors adjusted the definition by creating a subclassification, type I (perigraft endoleak) and type II (retrograde endoleak), both divided into subgroup A (inflow, no outflow) and subgroup B (both inflow and outflow). A further subclassification into type III endoleak (through fabric tears, graft disconnection or due to disintegration of the fabric) and type IV endoleak (associated with graft wall 'porosity') has been proposed recently[30]. The distinction between perigraft and retrograde endoleakage has also been made by others, who separated endoleakage from 'collateral perfusion'[17,31–33] or 'retroleak'[34].

The main finding of this analysis is that the total endoleak rate for all types of stent-grafts together was 24 per cent, subdivided into an immediate endoleak rate of 17 per cent and a delayed endoleak rate of 7 per cent. These figures are alarming because an endoleak implies that the aneurysm is not excluded from the circulation and so remains a danger. Consensus exists that perigraft endoleaks are hazardous and ruptures have been reported in affected patients whose endoleaks were followed[11,18,19,35,36]. In spite of a good alternative in the open repair of AAA, which has excellent long-term results, some surgeons and radiologists accept such incomplete endoluminal treatment. Side branch endoleaks rarely seem to lead to progressive aneurysm dilatation[37], but aneurysm growth with lumbar endoleaks has occasionally been reported[38].

Obviously the endovascular treatment of AAA is still an evolving field but, even if devices that are no longer available are excluded from the analysis and the most recent publications only are studied, the endoleak rate does not decrease; it remains at 25 per cent. The increase in endoleak rate between 1996 and the later period cannot be explained by the occurrence of delayed endoleaks during a longer follow-up period. Perhaps more challenging aneurysm morphology (for endovascular treatment), and an improved visualization and so better awareness of endoleaks might explain this finding. Many factors influence the occurrence of endoleakage[29]. Problems relating to patient selection, graft sizing, aortic morphology and technical difficulty during implantation could not be included in this analysis. Perhaps the analysis ought to be interpreted cautiously because of this but, on the other hand, it undoubtedly reflects current practice.

The configuration of the stent-graft seems to influence endoleak rate. This is especially true for the tube graft in relation to its distal stent attachment site, both in terms of endoleaks and delayed endoleaks. Most authors have indicated that the distal aortic cuff is rarely suitable for stent-graft fixation; thrombus at this site and future aortic cuff dilatation, unrelated to endoleaks, are frequently reported[4,22,27]. The absence of distal endoleaks in the aortounilateral group, on the other hand, underlines the suitability of the iliac artery as a better distal attachment site. A contralateral iliac occluder accompanies the aortounilateral stent-graft. While this device is responsible for 32 per cent of the endoleaks in this subgroup, the iliac position is relatively easily accessible for radiological intervention (e.g. a second occluder or coil embolization) and conversion to open repair for this type of leak has not been reported.

The difference between balloon-expandable and self-expandable stent-grafts at the distal attachment site can be explained by the technical difficulty of balloon inflation at the aortic bifurcation. While the self-expandable stent automatically accomplishes graft–aortic contact, the balloon-expandable stent may fail because of unsatisfactory stent deployment owing to insufficient balloon inflation limited by the diameter of the iliac artery. During follow-up, the static diameter achieved may prove insufficient for sealing in the face of progressive aortic neck dilatation[4,27,31]. If this happens, delayed endoleak occurs.

It is difficult to predict at the time of occurrence of an endoleak whether its presence will be associated with either aneurysm diameter increase, stabilization or reduction at follow-up. Reports of diameter increase of the aneurysmal sac and aneurysm rupture in the absence of endoleakage are of great concern[39,40]. After 24 months of follow-up, Stelter *et al.*[8] found that three of 19 aneurysms increased in diameter and that all three had had a previously sealed endoleak. These findings suggest that even a thrombosed endoleak can cause pressure within the sac, which may produce aneurysmal dilatation and possible rupture. It seems, therefore, that the definition of endoleakage should not focus on visualizing flow between the graft and the aneurysmal wall, but on the pressure caused by the endoleak and the effects of such pressure on the aneurysmal sac. Because the diameter decrease in the absence of an endoleak appears to take approximately 6 months to become significant[4,27,31,37], techniques should be developed to measure pressure non-invasively. If 'high-pressure' endoleaks can be distinguish from 'no-pressure' or 'low-pressure' endoleaks, the choice between intervention and observation will become more rational.

The Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery[41] advises surgeons to report initially transient (less than 48 h) and persistent (more than 48 h) endoleaks, and during follow-up to report persistent endoleaks (more than 6 months), aneurysm diameter increase (more than 0·5 cm) and intervention rate. However, no recommendations are made about reporting the site of endoleakage and any coexistent outflow tract. Only a small number of studies examined during this analysis presented the data on endoleakage in this way. In particular, information detailing the difference between transient and persistent endoleaks, and the change in aneurysm diameter with time was missing. For a better understanding of the course and effect of different types of endoleaks, reports of clinical studies about endovascular treatment of AAA should detail the following: number of endoleaks; site of origin (proximal or distal stent attachment site, through fabric, through modular components, occluder, lumbar arteries, inferior mesenteric artery, hypogastric artery, or unknown); presence of an outflow tract; time of occurrence (immediate – at the end of initial procedure, early – until discharge from the hospital, delayed – started during follow-up); imaging technique used for visualising the endoleak (angiography, computed tomography – either with early or delayed contrast admission, magnetic resonance imaging, duplex scanning); and diameter change of the aneurysm for the total stent-graft group, the subgroup with endoleakage and the subgroup without endoleakage, related to follow-up period. Ideally, this information should be supplied for each endovascular device and configuration, separately.

Major endovascular registries such as European Collaborators Group for Stent-graft Techniques for Abdominal Aortic Aneurysm Repair and Registry for Endovascular Treatment of Aneurysms collect all this information. Nowadays, results from these registries are being presented at conferences and will be published in the near future. With such information, we should understand more about the problems of endoleakage. For the present, however, one may conclude that endovascular treatment of AAA is still an evolving field; it is still accompanied by a significant number of potentially dangerous endoleaks. It is to be hoped in the future that better patient selection and improved devices will result from proper recording and appropriate analysis of clinical data.

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Periampullary diverticula and pancreaticobiliary disease

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Background: Periampullary diverticula (PAD) are extraluminal outpouchings of the duodenum arising within a radius of 2–3 cm from the ampulla of Vater. They are frequently encountered in elderly patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) and contribute to failure of ERCP. This review details the relationship of PAD to pancreaticobiliary disease and the influence of PAD on the management of patients.

Methods: The United States National Library of Medicine Medline database was searched for articles on and related to PAD published in English within the past 15 years. Major earlier works were also reviewed.

Results: The prevalence of PAD increases with age and could be as high as 27 per cent. PAD are associated with an incompetent sphincter of Oddi and colonization of bile duct with β-glucuronidase-producing organisms. PAD are implicated in the pathogenesis of pigment common bile duct stones, but there is no conclusive evidence to associate them with cholecystolithiasis or pancreatitis. PAD are a major cause of failure of ERCP, but success rates of more than 90 per cent have been achieved in specialist centres.

Conclusion: With an ageing population, there will be an increase in elderly patients with PAD and symptomatic pancreaticobiliary disease. Continuing improvements in radiological and endoscopic techniques should enable this vulnerable group to be treated effectively and safely.

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Introduction

Periampullary diverticula (PAD), also known as perivaterian or peripapillary diverticula, are extraluminal mucosal outpouchings of the duodenum arising adjacent to or containing the ampulla of Vater (major papilla) or intramural portion of the common bile duct (CBD)[1] (*Fig. 1*). Some PAD may penetrate into the head of the pancreas. Diverticula arising within a 2–3-cm radius of the ampulla, but not containing it, are referred to as juxtapapillary (juxta-ampullary) diverticula (JPD)[2,3]. A papilla that arises within a diverticulum is called an intradiverticular papilla (IDP).

This review explores the relationship between PAD and pancreaticobiliary disease, outlines the diagnostic and therapeutic problems caused by PAD and suggests alternatives to conventional endoscopic retrograde cholangiopancreatography (ERCP) in the management of affected patients. The rare intraluminal duodenal diverticulum, a defect in embryological development that usually presents with mechanical duodenal obstruction, has been excluded. Non-pancreaticobiliary complications of PAD such as haemorrhage, perforation and enterolith formation have not been discussed.

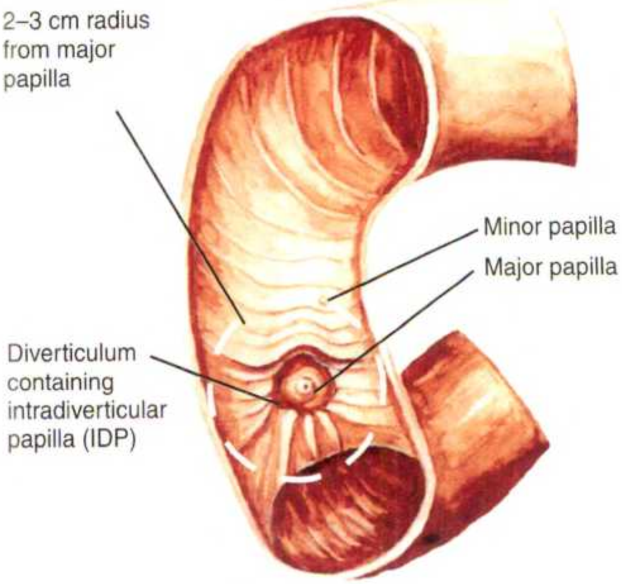
2–3 cm radius from major papilla
Minor papilla
Major papilla
Diverticulum containing intradiverticular papilla (IDP)

Fig. 1 Oblique view of the duodenum demonstrating an intradiverticular papilla. Diverticula arising within a 2–3-cm radius of the major papilla but not containing it are called juxtapapillary diverticula

Historical note

The earliest description of a duodenal diverticulum is attributed to Chomel who, in 1710, reported a diverticulum that contained 22 calculi, presumably of biliary origin[4]. Baldwin[5] was the first to demonstrate emptying of the CBD into a duodenal diverticulum in five cases at autopsy. The insertion of the duct was adjacent to the neck of a diverticulum in two cases. Case[6] is credited with the first radiographic demonstration of a duodenal diverticulum, and Lemmel[7] was the first to suggest a relationship between pancreaticobiliary disease and duodenal diverticula when he described two symptom complexes, which he thought were characteristic of, but not specific for, PAD. He described an association between the presence of PAD and the occurrence of liver and bile duct disease in combination with damage to the pancreas and pancreatogenic diarrhoea, and coined the term 'papillensyndrom'. The other symptom complex was non-specific and consisted of sudden onset of vomiting in association with abdominal colic without any relation to meals.

Prevalence

It is difficult to ascertain the true prevalence of duodenal diverticula in the general population; reported rates vary between 0·16 and 27 per cent[1,4,8–19]. The prevalence on barium meal examination ranges from 0·16 to 6 per cent and a rate of 23 per cent has been reported at autopsy[15]. The prevalence of PAD at ERCP ranges from 5 to 27 per cent, the average being around 17 per cent.

Prevalence increases with age[1,4,9,12,15–21] and quoted prevalence rates are therefore dependent on the age of the population under study. Diverticula are exceptional below the age of 40 years and the mean/median age at which PAD are diagnosed ranges from 56 to 76 years. The age-related prevalence in patients undergoing ERCP is shown in *Table 1*. PAD may be slightly more common in women than in men and most series quote a male : female ratio of 1 : 1 to 1 : 1·5. About 70–75 per cent of all duodenal diverticula are periampullary[2,22] and, of the latter, JPD outnumber IDP (*Table 2*).

The relatively low prevalence rate on barium meal has commonly been attributed to a failure to report or demonstrate many diverticula. However, in a study in which all patients with PAD on ERCP were subjected to a barium meal examination, the sensitivity of barium meal in diagnosis of duodenal diverticula was 83 per cent[13]. Small diverticula may be missed on barium meal examination, but this does not explain the more than fourfold increase in prevalence of duodenal diverticula at ERCP, especially since most barium meal series include diverticula arising in all four parts of the duodenum and not just PAD[8,9]. Side viewing duodenoscopy is a better method of demonstrating duodenal diverticula than barium meal and hypotonic duodenography. The striking difference in prevalence is probably because patients undergo ERCP when they have biliary or pancreatic symptoms while a barium meal was often used to investigate non-biliary upper gastrointestinal symptoms in the pre-endoscopic era.

Pathogenesis

PAD are usually 'acquired' in middle age and may be the end result of disordered duodenal motility. Histologically, the walls of the diverticula consist of mucosa and submucosa with scattered smooth muscle. They resemble the pulsion diverticula seen elsewhere in the gastrointestinal tract.

A congenital factor may be involved as the diverticula may originate from localized defects in the duodenal musculature arising from abortive attempts to form a supernumerary pancreas[25]. Advancing age, progressive

Table 1 Change in prevalence of periampullary diverticula with age in patients undergoing endoscopic retrograde cholangiopancreatography

Age group (years)	No. with PAD	No undergoing ERCP	Prevalence of PAD (%)
< 50	78	1266	6·2
50–59	120	810	14·8
60–69	167	752	22·2
70–79	174	567	30·7
≥ 80	99	320	30·9
Overall	638	3715	17·2

Data pooled from six large studies[4,12,14,16,18,19] in which the age-related prevalence of periampullary diverticula (PAD) was determined at endoscopic retrograde cholangiopancreatography (ERCP)

Table 2 Relative prevalence of periampullary diverticula according to location

Reference	Year	Intradiverticular papilla (%)	Juxtapapillary diverticulum (%)	Total no. with PAD
Eggert *et al*[2]	1982	25·4	74·6	71
Lotveit *et al.*[4]	1988	26·4	73·6	121
Vaira *et al*[1]	1989	6·8	93·2	308
Boender *et al.*[23]	1994	15·8	84·2	95
Jang *et al.*[24]	1995	45·0	55·0	20
Lobo *et al.*[17]	1998	42·0	58·0	100

PAD, periampullary diverticula

weakening of intestinal smooth muscle and increase in intraduodenal pressure may encourage outpouching of the duodenum at the site of these defects[25]. This theory has been substantiated by Suda *et al.*[26] who demonstrated that in 14 of 18 cases of duodenal diverticula penetrating the pancreas, the penetration occurred at the line of embryonal fusion of the dorsal and ventral pancreas. In the remaining four cases, the site of penetration in the ventral pancreas was close to the fusion line. They also confirmed that diverticula arise at weak spots in the duodenal wall, i.e. the perivascular connective tissue sheath and the site of entry of the CBD and pancreatic duct.

More recently, it has been demonstrated that migrating motor complexes in the duodenum occur more frequently in patients with PAD and that maximal duodenal contraction pressure is increased in these patients[3]. Furthermore, plasma concentrations of motilin and somatostatin are high in patients with PAD[3]. This might contribute to a prolonged interprandial increase in intraduodenal pressure, thereby predisposing these patients to the development of PAD, but it has not been established whether the raised level of plasma motilin and somatostatin is a cause or an effect of PAD.

Biliary manometry

Ruggero Oddi described the presence of a sphincter at the terminal end of the CBD in 1887 and suggested its role in the regulation of bile flow into the duodenum. Sphincter of Oddi pressures have been evaluated using manometric techniques. Baseline sphincter pressures are higher than those in the duodenum and CBD in normal subjects. Phasic activity is superimposed on the sphincter and these phasic waves are normally propagated to the duodenum[27].

An early study reported that sphincter motor activity is similar in patients with and without PAD[28]. However, the patients studied were premedicated with atropine and pethidine, both of which influence sphincter function. Endoscopic single-lumen biliary manometry performed on patients with PAD, with choledocholithiasis without PAD and normal controls demonstrated no significant difference in sphincter basal pressure, frequency and amplitude between the three groups[29]. Diazepam, a drug known not to influence sphincter of Oddi function, was used to sedate patients in this study.

Comparable CBD pressures have also been demonstrated in patients with PAD and normal controls[30]. However, muscular tone, contractile activity and total rhythmic variation of the sphincter during saline infusions are significantly less in patients with PAD suggesting sphincter dysfunction[30]. Papillary dysfunction and diminution in sphincter tone in patients with PAD has been confirmed in other studies[31–34]. A recent study has shown that intrabiliary residual pressure and biliary resistance are higher in those with PAD than in those without diverticula, but these differences are not statistically significant[35]. It has been hypothesized that sphincter dysfunction is caused by prolonged mechanical compression of the terminal CBD resulting from repeated distension of PAD during periods of increased intraduodenal pressure[33].

Biliary manometry is largely a research technique at present and is unlikely to become generally available as a routine clinical investigation in the near future. Its role in the management of PAD is not clear.

Bacterial colonization of the biliary tract

PAD, like diverticula elsewhere in the gastrointestinal tract, form blind pouches that favour bacterial colonization and overgrowth. Bacteriobilia is commonly associated with PAD[2,36,37]. The prevalence of bacteriobilia increases with age and is higher in the presence of PAD. Organisms cultured from samples taken from the diverticula are identical to those grown from the bile. *Escherichia coli*, *Streptococcus faecalis*, *Proteus* spp., *Klebsiella* spp. and anaerobes are the most common organisms isolated. Bacteriobilia is less likely to be found as the distance of the diverticulum from the ampulla increases[2].

Skar *et al.*[36] found that patients with CBD stones and PAD are much more likely to have β-glucuronidase-producing bacteria in the bile than patients with common duct stones but no diverticula ($P < 0{\cdot}01$). Moreover, those with PAD have significantly higher β-glucuronidase activity in the bile than those without diverticula. The same group[37] also showed that patients with PAD have significantly higher duodenal bacterial counts than those without diverticula ($P < 0{\cdot}01$). Once again, the most commonly isolated organisms are Enterobacteriaceae and faecal streptococci in the presence of PAD. Interestingly, Gram-positive cocci are the organisms most frequently isolated in the absence of PAD.

In another study positive bile cultures were obtained in 78 per cent of patients with PAD but in only 42 per cent of those without diverticula ($P < 0{\cdot}01$)[38]. Bacteria were found in the bile of 89 per cent of patients aged 60 years or more and in 63 per cent of patients aged less than 60 years with PAD ($P < 0{\cdot}05$).

Relationship of periampullary diverticula to biliary disease

Cholecystolithiasis has been suggested to occur more frequently in association with PAD[10,11,15,18,39], but this finding is not supported by other studies[16,19,40,41] and the association is more likely to be incidental than causal. Interestingly, in one study[40], although there was no difference between the presence or absence of PAD and the overall frequency of cholecystolithiasis, gallbladder stones were significantly more common with PAD 20 mm or more in diameter than with smaller PAD. There is evidence to implicate PAD in the pathogenesis of pigment CBD stones[15,39,42–45] and a possible mechanism resulting in a lithogenic milieu within the CBD is proposed in *Fig. 2*. PAD are present in a significantly greater number of patients with choledocholithiasis than in patients with normal ducts at ERCP[19,21,41]. After adjusting for age, those with choledocholithiasis are 2·6 times more likely to have PAD than those without CBD stones[14]. CBD diameter may be greater with PAD than without PAD, but such a difference has not attained statistical significance[14]. However, using stepwise logistic regression analysis, bile duct diameter has been shown to be an independent predictor of the presence of PAD[21].

Primary and recurrent CBD stones are much more common with PAD than without the condition[18,39,45–47]. In a study of 101 patients who developed biliary or pancreatic symptoms after being asymptomatic for at least 2 years following a cholecystectomy for gallstone disease, with or without CBD exploration, the probability of finding CBD stones was 88 per cent with PAD and 32 per cent without[46]. This, however, was a highly selected group of patients and the figures do not necessarily reflect routine clinical practice. Cholecystectomy in patients with PAD does not prevent the development of recurrent CBD stones and PAD predispose patients to primary rather than secondary CBD stones[18,47]. For patients with radiologically diagnosed duodenal diverticula, the cumulative probabilities of developing biliary tract disease subsequent to cholecystectomy are 4, 6 and 10 per cent at 5, 10 and 15 years respectively[48]. A recent study has questioned this relationship because, after adjusting for age and sex, PAD do not appear to influence the development of choledocholithiasis[16]. Although Leivonen *et al.*[22] noted that CBD stones are present more often in patients with PAD than in those without PAD, they were unable to show a clear correlation between the presence of PAD and the occurrence of biliary disorders.

There are anecdotal reports suggesting that PAD may cause extrinsic compression of the lower end of the CBD and result in obstructive jaundice[49,50]. Recent studies[17,22] have shown that a significant proportion of patients with PAD and biliary symptoms have normal biliary and pancreatic ducts. It has been proposed that the PAD may be responsible for transient biliary symptoms and alterations in liver function[17]. Sphincteric dysfunction, low-grade cholangitis and intermittent extrinsic compression brought on by entry of food into the diverticulum may explain this phenomenon.

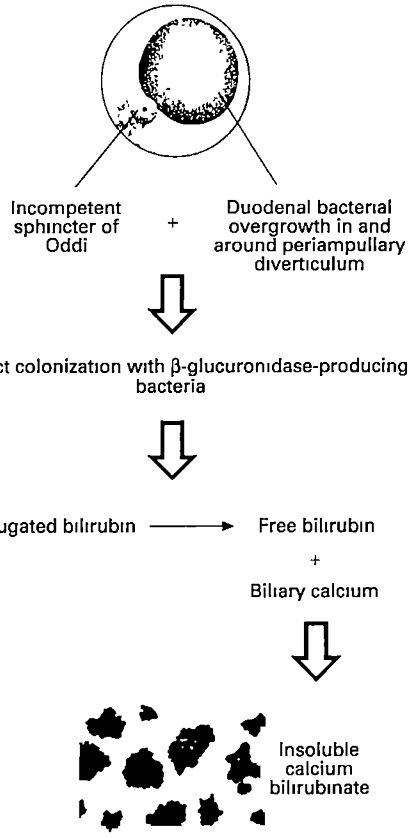
Incompetent sphincter of Oddi
+
Duodenal bacterial overgrowth in and around periampullary diverticulum
Bile duct colonization with β-glucuronidase-producing bacteria
Conjugated bilirubin
Free bilirubin
+
Biliary calcium
Insoluble calcium bilirubinate

Fig. 2 Pathogenesis of pigment common bile duct stones in patients with periampullary diverticula

Relationship of periampullary diverticula to pancreatic disease

There are case reports and anecdotal accounts implicating PAD in the pathogenesis of acute and chronic pancreatitis[13,20,51]. PAD were found in 23 per cent of 75 patients with acute pancreatitis in a retrospective study while only 4 per cent of patients in a comparable control group had PAD[52]. In a study of 470 consecutive patients undergoing ERCP, recurrent acute pancreatitis or chronic pancreatitis was found in 26 per cent of patients with PAD and in 14 per cent of those without PAD ($P < 0{\cdot}05$)[11]. Psathakis *et al.*[20] found that five of 50 patients with PAD had features of pancreatitis. However, the relationship with pancreatitis remains tenuous as biliary calculous disease is more common in PAD. It is debatable whether the pancreatitis is caused by the PAD *per se* or by the associated biliary calculi.

Distension of a diverticulum with inspissated food may cause compression of the pancreatic duct and result in pancreatitis[53,54]. Ampullary dysfunction secondary to PAD has also been implicated in the pathogenesis of pancreatitis[54]. A recent study has suggested that PAD should be included as a factor in the aetiology of acute pancreatitis in the elderly, and that the presence of PAD should be excluded before diagnosing idiopathic pancreatitis[55]. No significant difference was noted when the proportion of patients with PAD and gallstone pancreatitis was compared with that with gallstone pancreatitis and no PAD (72 *versus* 73 per cent; $P = 0{\cdot}9$). However, when patients with idiopathic acute pancreatitis were analysed, there was a significantly higher incidence in patients with PAD than in those without the condition (14 *versus* 2 per cent; $P = 0{\cdot}04$)[55].

Leivonen *et al.*[22] found that patients with PAD developed idiopathic pancreatitis twice as often as those without the condition (11 *versus* 6 per cent), but this difference was not statistically significant. Other studies have been unable to establish that patients with PAD develop pancreatitis more frequently than those without diverticula[10,13]. The data associating PAD and pancreatitis are limited; there is insufficient evidence to state categorically that PAD contribute significantly to the pathogenesis of pancreatitis.

Pancreatitis in the elderly is a problem of increasing occurrence and is associated with severe complications. Many of these patients will have PAD and an appreciation of the possible relationship between pancreatitis, PAD and CBD stones may lead to improved care for this high-risk group.

Diagnostic confusion

Ignorance of the presence of PAD may lead to confusion in interpreting radiological images of the biliary tree. PAD can produce apparent filling defects in the lower end of the CBD that may be mistaken for periampullary tumours on percutaneous transhepatic cholangiography (PTC) and operative cholangiography[56,57]. Prominent mucosal folds around the diverticular neck – the mucosal rosette – may be the cause of these findings[57]. PAD have also been mistaken for periampullary tumours on ultrasonographic examination because they produce a 'pseudo-mass' effect[58]. Large diverticula distended with fluid may simulate a pancreatic pseudocyst or peripancreatic fluid collection on ultrasonography[59], and air within a diverticulum creates artefacts at the lower end of the CBD.

Filling defects produced by PAD on PTC, ERCP and operative cholangiography may be confused with CBD stones[60,61] and lead to unnecessary CBD exploration and endoscopic sphincterotomy, with occasionally an increased morbidity[61]. The possibility of a PAD-related artefact at the lower end of the CBD should, therefore, be borne in mind when interpreting any type of bile duct imaging.

Problems with endoscopic retrograde cholangiopancreatography

The presence of PAD can make ERCP a technically demanding exercise (*Fig. 3*). Only a few studies exist which address the success rate of ERCP in patients with PAD; this is usually lower than that in patients without PAD (*Table 3*). *Table 3*, however, also illustrates that it is possible to achieve high success rates for ERCP in patients with and without duodenal diverticula[12,47]. It must be emphasized that all procedures in one of the studies were carried out by a single operator and that patients in whom the ampulla was not located or in whom a diagnosis was arrived at on endoscopic examination were excluded[12]. Impressive results were also attained by Vaira *et al.*[1], but the 94 per cent success rate was achieved only at third attempt and only 7 per cent of the patients had IDP. Only one study[17] cites differential cannulation success rates in patients with JPD and IDP (78 *versus* 38 per cent

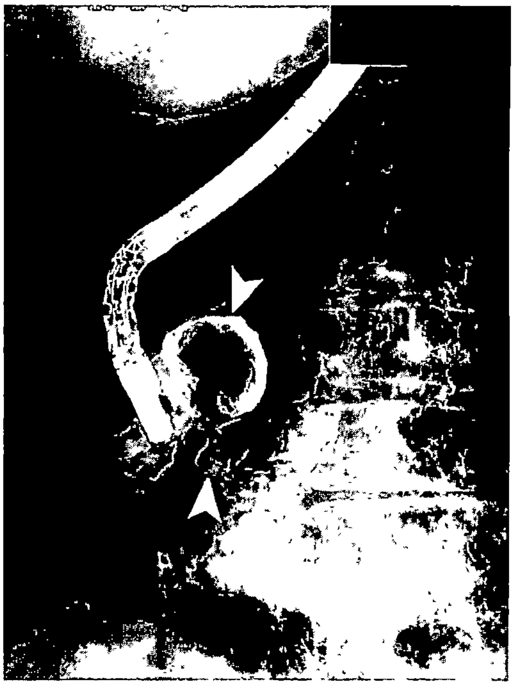

Fig. 3 Cannulation at endoscopic retrograde cholangiopancreatography was unsuccessful and two periampullary diverticula (arrows) have been outlined with contrast

Table 3 Success rates of endoscopic retrograde cholangiopancreatography in patients with and without periampullary diverticula

		Patients without PAD		Patients with PAD		
Reference	Year	No	Success rate (%)	No	Success rate (%)	*P*
Kirk and Summerfield[10]	1980	717	80	38	60	< 0·02
Lintott *et al.*[60]	1981	—		38	55·3	—
Vaira *et al.*[1]	1989	2150	96·7*	308	76·9†	< 0·05
				308	94·2*	
Chang-Chien[12]	1987	1090	91·0	153	91·5	> 0·05
Hall *et al.*[47]	1990	546	98·0	95	94·7	0·06§
Leivonen *et al.*[22]	1996	320	75·0‡	84	77·3‡	0·65§
Lobo *et al.*[17]	1998	1102	92·7	109	62·4	< 0·0001

*Third attempt, †first attempt. ‡Success rate rose to 93·1 per cent in patients without periampullary diverticula (PAD) and to 84·5 per cent in patients with PAD ($P = 0{\cdot}013$§) if single duct (bile or pancreatic) cannulation was considered the endpoint. §*P* values calculated by the authors of this review using the χ^2 test

respectively), but the consensus is that ERCP is much more difficult to perform in patients with IDP than with JPD[1,62,63].

Early studies recommended that PAD should be considered a relative contraindication to endoscopic sphincterotomy because of the potential risk of perforating the diverticulum[64] but later work has shown that success rates are similar in patients with and without PAD[1,62]. The overall success of sphincterotomy was 98 per cent in patients without PAD and 95 per cent in those with PAD ($P < 0{\cdot}05$) in a large single-centre study; however, there was no difference between the groups if only those patients in whom cholangiography was successful were included[1]. Similar success rates for endoscopic sphincterotomy (93 *versus* 91 per cent in patients without and with PAD respectively) have been obtained in smaller groups of patients[62], but it must be reiterated that sphincterotomy is not an easy procedure in the presence of PAD and often fails[65].

Haemorrhage is the most frequent complication of endoscopic sphincterotomy in the face of PAD[1,23,66]. Logistic regression analysis has shown that the presence of PAD is an independent variable that predicts bleeding after sphincterotomy[67], but most authors do not feel that bleeding occurs more often in these patients than in the general population[1,23,66,68]. Although some authors still consider IDP to be a relative contraindication to precut or endoscopic sphincterotomy[23], most large studies have not documented an increased risk of perforation of the diverticulum[1,66,68,69].

There is no significant difference between the overall procedure-related morbidity and mortality rates in patients with and without PAD[1,23]. Morbidity and mortality figures of 5·2 and 0·9 per cent *versus* 4·0 and 0·7 per cent have been obtained in patients with and without PAD respectively[1]. Corresponding rates of 11·6 and 0 per cent *versus* 2·7 and 0 per cent have been obtained in a recent study[23].

Therapeutic laparoscopic and endoscopic skills are advancing rapidly so that even very elderly patients with PAD and 'surgical complications' will be amenable to curative treatment. With modern endoscopic techniques, experienced operators should have a high success rate for diagnostic ampullary cannulation and the complication rate of ERCP should be no greater than that for comparable patients without PAD.

Surgical procedures for periampullary diverticula

Earlier this century surgical diverticulectomy (excision of the diverticulum and repair of the duodenum), or even simple invagination of the diverticulum without excision, was frequently carried out for non-specific symptoms[70,71], many of which in retrospect were probably pancreaticobiliary in origin. Diverticulectomy is a relatively simple procedure for anterior diverticula. Posterior diverticula may be tackled after Kocherizing the duodenum; a careful and skilful dissection is required to excise diverticula penetrating the pancreas. Today the commonest indications for surgery are bleeding and perforation, complications not discussed further in this review. Whether pancreaticobiliary symptoms can be 'cured' by a direct surgical attack on PAD remains very controversial.

Sporadic case reports and short clinical series still occur which endorse direct surgical intervention on the diverticulum for patients with biliary symptoms secondary to PAD. Based on an experience of two cases, diverticulectomy is recommended by some in jaundiced patients with PAD[72]. In another series, diverticulectomy was performed in 12 of 18 patients[73], combined with a transduodenal sphincteroplasty in 11, none of whom had recurrence of symptoms over a mean follow-up of 3 years. Five of the patients who did not have a diverticulectomy and one who had a diverticulectomy without a transduodenal sphincteroplasty presented with recurrent pancreaticobiliary symptoms 3–12 months after surgery. Extended transduodenal sphincteroplasty for CBD stones associated with PAD has been shown to be a safe procedure in nine patients and has been proposed as an alternative to choledochoduodenostomy[74].

In one series of three patients Roux-en-Y duodenojejunostomy was performed for PAD presenting with pancreaticobiliary disease[75]. The aim of the operation was to isolate the diverticulum from the food stream, thereby eliminating stasis of food within the diverticulum and resultant cholangitis and pancreatitis. This procedure also resulted in decreased concentrations of motilin and somatostatin[3]. Vassilakis *et al.*[76] have combined the duodenojejunostomy with a choledochojejunostomy in five patients and claim improved results because of diversion of bile and food from the diverticulum.

Diverticuloplasty has also been performed in five patients with PAD[77]. Four had bile duct or pancreatic duct obstruction and the fifth had chronic abdominal pain. Three patients had significant intraoperative and early postoperative complications, but all were free from pancreaticobiliary symptoms during a mean follow-up of 7 years.

Surgical procedures on PAD are of no proven long-term benefit in patients with pancreaticobiliary symptoms and are not without major morbidity and the occasional death. It is not possible to compare this morbidity with that following ERCP because most reports are of isolated cases or very small selected series. It is unlikely that open surgical operations on PAD will be carried out any more frequently in the future; however, improvements in laparoscopic and endoscopic therapy hold much promise.

Present options and future directions

The main concern for the gastroenterologist investigating or treating patients with PAD is the relatively high failure rate of diagnostic and therapeutic ERCP. The fact that most patients with PAD are elderly has limited diagnostic and therapeutic options in the past. PTC has been used extensively as an alternative to ERCP for both diagnostic and therapeutic purposes. Combined ERCP/PTC techniques have been proven to increase the success rate of non-surgical treatment in poor-risk patients with benign and malignant diseases of the biliary tract[78].

A catheter with an external steering device has been used to make ERCP easier in PAD[79]. Sherman *et al.*[80] have overcome the problem by using a stone retrieval balloon that has a channel for introduction of a guidewire. The catheter is inserted through the papilla into the common pancreaticobiliary channel and the balloon inflated. Traction applied to the catheter pulls the papilla on to the rim or out of the diverticulum, thereby bringing it into optimal view. The manoeuvre also straightens the bile duct and limits movement of the papilla, facilitating introduction of the guidewire into the CBD. The balloon catheter may then be removed and a sphincterotome inserted over the guidewire.

The use of a duodenoscope with a large operating channel, permitting introduction of biopsy forceps and a cannula together, has been described[81,82]. The mucosa of the diverticulum next to the papilla is grasped with the forceps and the papilla fixed in front of the operating channel, thereby facilitating insertion of the cannula.

The 'tuteur transcystique-transpapillaire' technique[83] involves the insertion of a transcystic–transpapillary drain at the time of laparoscopic or open cholecystectomy. The stent traverses the papilla and enters the duodenum, thereby providing bile drainage and facilitating subsequent ERCP and stone extraction.

Stent-guided sphincterotomy is recommended in patients with PAD as the chances of perforating the diverticulum are reduced[84]. Farrell *et al.*[85] succeeded in a patient with an exophytic ampulla adjacent to a large duodenal diverticulum by snaring the ampulla flush with the duodenal wall after encircling the entire base of the ampulla. A difficult cannulation is thus made easy by performing an endoscopic papillectomy. Fogel *et al.*[86] describe a useful technique of biliary cannulation in patients with IDP. Initial insertion of a pancreatic duct stent helps elevate the papilla out of the diverticulum, thereby facilitating safer needle-knife sphincterotomy to achieve biliary cannulation. Doubtless many other successful endoscopic 'tricks' have gone unreported.

The evolving techniques of spiral computed tomography, endoscopic ultrasonography and magnetic resonance cholangiopancreatography (MRCP) are proving to be useful diagnostic alternatives to ERCP. It is envisaged that MRCP will reduce the indications for diagnostic ERCP and that ERCP will be reserved for clarification of MRCP results in some cases and for therapeutic purposes[87]. This may be particularly true in patients with PAD in whom ERCP is difficult. ERCP for such patients is best left in the hands of experienced endoscopists who have good success rates. There remains a need, however, for interdisciplinary teamwork between medical endoscopists, surgeons and interventional radiologists in the management of patients with PAD.

Acknowledgements

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TWO ARTICLES FOR COMPARISON

ARTICLE A

APACHE II score in massive upper gastrointestinal haemorrhage from peptic ulcer: prognostic value and potential clinical applications

This study examined the prognostic value of the APACHE II scoring system in patients undergoing emergency operations for bleeding peptic ulcer. There were 96 operations for gastric ulcers and 58 for duodenal ulcers. The mean scores in survivors and in patients who died were 10·8 and 17·5 respectively. None of the 66 patients with an APACHE II score <11 died, while the mortality rate in those scored >10 was 22 per cent. In patients scored >10 non-resective procedures carried less risk of mortality than gastrectomy The APACHE II score is useful when measuring the severity of the acute disease and predicting the outcome in these patients. If used in daily practice it may assist the surgeon in stratifying patients into a low-risk group (score <11) in which major operations are well tolerated and outcome is favourable and a high-risk group (score >10) in which the risk of mortality is high and the performance of procedures of lesser magnitude is probably more likely to improve survival.

Keywords: APACHE II, outcome prediction, upper gastrointestinal haemorrhage, emergency gastroduodenal operations

The procedure of choice for the surgical control of a bleeding peptic ulcer is controversial. While some authors advocate the use of truncal vagotomy and antrectomy (TV+A) for a bleeding duodenal ulcer, others claim that truncal vagotomy and a drainage procedure (TV+D) is safer. The same argument involves the management of bleeding gastric ulcers. Whilst partial gastrectomy continues to be the procedure of choice in many major centres, others attribute lower mortality rates to more conservative operations such as TV+D or simple undersewing of the ulcer alone.

The comparison of results is distorted by the fact that sicker patients are usually selected for the more conservative operations. Thus, for example, McGuire and Horsley, operating on bleeding duodenal ulcers, cited a mortality rate of 21 per cent for TV+A and 45 per cent for TV+D. It is widely....

Written by: M. Schein and G. Gecelter
Published: Br J Surg 1989; 76: 733–6

ARTICLE B

APACHE II score in massive upper gastrointestinal haemorrhage from peptic ulcer

Abstract

This retrospective study examined the prognostic value of the APACHE II scoring system in patients undergoing emergency operations for bleeding peptic ulcer. Between 1980–1997 there were 228 patients who had operated emergency for bleeding peptic ulcer. There were 57 operations (25%) for gastric ulcers and 171 (75%) for duodenal ulcers. There were 48 (21·2%) female, 180 (78·9%) male and the median age was 46·0 ± 16·4 (range 15–81) In the group who had operated for gastric ulcer male/female ratio was 47/10 and the median age was 49·4 ± 16·4. In the group who had operated for duodenal ulcer male/female ratio was 133/38 and the median age was 44·8 ± 16·3. The mean APACHE II scores in survivors and in patients who died were 5·29 and 9·27 respectively. In patients who had high APACHE II scores; vagotomy + drainage procedures carried less risk of mortality than vagotomy + resection.

If used in daily practice it may assist the surgeon in stratifying patients into a low-risk group in which major operations are well tolerated and outcome is favourable and high-risk group in which the risk of mortality is high and the performance of procedures of lesser magnitude is probably more likely to improve survival.

Keywords: APACHE II, upper gastrointestinal haemorrhage, emergency gastroduodenal operations

Introduction

The procedure of choice for the surgical control of a bleeding peptic ulcer is controversial. While some authors advocate the use of truncal vagotomy and antrectomy (TV+A) for a bleeding duodenal ulcer, others claim that truncal vagotomy and a drainage procedure (TV+D) is safer. The same argument involves the management of bleeding gastric ulcers. Whilst partial gastrectomy continues to be the procedure of choice in many major centres, others attribute lower mortality rates to more conservative operations such as TV+D or simple undersewing of the ulcer alone.

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Submitted by: Okan Dalyan, Haluk Demiryurek, Fatih Kaya, Bulent Belevi of the University of Cukurova, Dept of Gen Surgery, Adana, Turkey

To: Digestive Surgery–December 1998

It was by chance that Dr Marcus Büchler, Editor of *Digestive Surgery*, sent Article B to be refereed by one of the authors of Article A, who recognized the text. If not spotted by this referee, the article may well have been published in *Digestive Surgery* and would have represented a form of plagiarism. The paper from Turkey presumably used local data within the total text and results framework of Article A.

The first author of Article B has expressed sincere regrets at this incident and offers "insufficiency of English" and "definitely my aim was not plagiarism" as explanations. The situation was compounded by the fact that Doctors Demiryurek, Kaya and Belevi did not see and agree the article before submission. This is confirmed by correspondence from all alleged authors of Article B. The editors of the *BJS* and *Digestive Surgery* believe that Drs Demiryurek, Kaya and Belevi were unaware of these matters until alerted to the situation and are, therefore, innocent of any publishing misdemeanour.

BJS and *Digestive Surgery* are dismayed to be involved in such a situation. This article appears in both Journals as an agreed statement between the editors, higher officers and publishers, to be read by the surgical scientific community. The recommendations following this incident are:

(i) If your first language is not English, do seek help in the writing of your paper. Do not 'lift' text from existing papers into your own manuscript without appropriate acknowledgement;

(ii) As a supervisor of trainees, be responsible for advising and guiding first attempts at surgical writing;

(iii) It is best practise to submit signed declarations of authorship from all named authors at the time of submission.

The *BJS* and *Digestive Surgery* will not condone any examples of this type of behaviour and will declare such events in their pages and send copies of these notices to host universities, hospitals and institutions. These Journals support the stance of other editors and journals in attempts to reduce these instances to a minimum through groupings such as The Committee on Publication Ethics[1,2].

J. R. Farndon
Editor – for *BJS*

M. Büchler
Editor – for *Digestive Surgery*

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1 Michael JG Farthing. Coping with fraud. *Lancet* 1998; **352** (Suppl IV). 11.
2 Michael Farthing. Gut in 1999. *Gut* 1999; **44**· 1 (Editorial).

For this quarter's digest, Professor Christian Herfarth and Dr Thomas Lehnert have selected the best from the July to September 1998 issues of *Der Chirurg*. A digest for the BJS for the same period, written by Mr Colin Johnson, appears in the German journal.

Metastatic breast cancer

Surgery for recurrent disease is widely accepted for local and distant metastases from colorectal carcinoma. Considerable numbers of patients have been treated, and operative risk and long-term prognosis are well established. Fewer data exist for other solid tumours, either because they are rare or because recurrent disease does not lend itself to another attempt at curative operation. However, some experience has been gained over the years. In a retrospective analysis, surgeons from Vienna examined their experience with surgical treatment of pulmonary metastases from breast cancer in 96 patients[1]. During a 20-year period (1977–1997), 28 patients with a median age of 41 years had curative resection, 34 had incomplete resection and 34 had no resection. For resection of pulmonary metastases 52 patients required atypical resection, nine had lobectomy and one patient required pneumonectomy. There were no perioperative deaths. Median disease-free and overall survival after complete resection ($n = 28$) was 24 and 63 months respectively. The 5- and 10-year survival rate was estimated at 80 and 60 per cent respectively. The authors observed that the location and number of pulmonary metastases were not of prognostic relevance. In patients with metastatic breast cancer, pulmonary resection therefore appears justified if all gross disease is resectable.

Adjuvant treatment after curative resection of hepatic metastases from colorectal cancer

Adjuvant treatment appears to confer a small survival advantage to patients with curatively resected Union Internacional Contra la Cancrum (UICC) stage III colon cancer and to patients with cancer of the rectum. To date no randomized trial has demonstrated conclusively that adjuvant therapy is also beneficial to patients with completely resected liver metastases. A group from Aachen has reviewed its experience with adjuvant intra-arterial chemotherapy in 50 patients in whom liver metastases from colorectal cancer were completely resected compared with 59 patients who did not receive intra-arterial chemotherapy[2]. Evaluation of potential risk factors indicated that patients receiving adjuvant treatment had a higher percentage of multiple metastases, but other prognostic variables were similarly distributed between the two groups. Five of 109 patients died after operation (5 per cent). Chemotherapy consisted of six one-monthly courses of 5-fluorouracil, mitomycin C and, from 1993, leucovorin.

Postoperative port-related complications were frequent: 19 of 50 patients required reoperation. Overall 49 complications were observed in 36 patients in the chemotherapy group. Twelve patients required port revision and the port was explanted in five. Treatment had to be discontinued in nine patients (18 per cent) because of complications. No significant differences were noted between study groups regarding the frequency of local or distant metastases. Overall survival appeared to be improved by adjuvant chemotherapy initially, but 5-year survival was 21 per cent in the adjuvant group compared with 24 per cent in the control group. The authors conclude that adjuvant intra-arterial chemotherapy following curative resection of hepatic metastases from colorectal cancer may delay recurrence, but does not affect long-term survival. Because of the high complication rate and lack of long-term benefit, routine use of intra-arterial chemotherapy cannot be recommended presently.

Neoadjuvant radiotherapy for rectal cancer

In a prospective randomized trial a group from Dresden has studied the effect of neoadjuvant radiotherapy in carcinoma of the rectum[3]. Between 1987 and 1993, 93 patients with histologically proven carcinoma of the rectum were randomized to short-term preoperative radiation (five doses of 3·3 Gy) followed by operation within 48 h ($n = 47$) or no neoadjuvant radiotherapy ($n = 46$). Postoperative radiotherapy was given to patients with T_4 tumours, node-positive tumours or incompletely resected tumours. No patient received adjuvant chemotherapy. Patients were eligible for randomization, if clinical evaluation indicated complete resectability of the tumour. Patients were stratified by age. More patients in the non-irradiated group required abdominoperineal resection ($n = 27$) than in the irradiated group ($n = 20$). Complete (R_0) resection of the tumour was achieved in 37 of 46 patients who did not receive neoadjuvant radiotherapy and in 40 of 47 irradiated patients ($P = 0·6$). Anastomotic insufficiency was recorded in nine patients (four irradiation and five no irradiation) and five patients (three irradiation, two no irradiation) died after operation.

The median follow-up was 3·8 (range 0·2–8·3) years. Local recurrences developed in five of 40 after neoadjuvant radiotherapy and in nine of 37 in the non-irradiated group ($P = 0{\cdot}08$). The median time to local recurrence was 1·9 years without preoperative radiotherapy and 3 years with short-course neoadjuvant irradiation. Distant metastases were detected in nine of 37 patients in the control group and in five of 40 patients in the irradiated group. Overall 5-year survival was 38 per cent for all patients and was 70 per cent for UICC stage I, 52 per cent for stage II, 19 per cent for stage III and zero for stage IV disease. Survival was significantly better for patients receiving preoperative radiotherapy (49 per cent at 5 years) compared with controls (28 per cent at 5 years) ($P = 0{\cdot}027$). Multivariate analysis, however, determined age ($P = 0{\cdot}0003$), complete resection ($P = 0{\cdot}01$) and UICC stage ($P = 0{\cdot}001$) as prognostic factors. Neoadjuvant treatment had no significant influence on survival ($P < 0{\cdot}08$).

Acute necrotizing pancreatitis

Acute necrotizing pancreatitis remains a serious clinical condition with respectable hospital mortality rates requiring consistent cooperation between surgeons, anaesthetists and gastroenterologists. Randomized trials have shed some light on the optimal therapy of pancreatitis. However, many questions regarding the clinical management of acute necrotizing pancreatitis remain unresolved. Surgeons and anaesthetists from Duisburg have conducted a mail survey to determine current clinical practice[4]. Twenty-eight units with a record of clinical and academic interest in the treatment of acute pancreatitis were asked to complete a 12-item questionnaire.

Answers were received from all 12 surgical departments, from two of six gastroenterological departments and from nine of ten anaesthesiological departments. Although they recognized the lack of hard evidence, 14 of 23 respondents to the questionnaire would use antibiotics prophylactically. Similarly 15 call for endoscopic extraction of biliary stones in the initial phase of the disease. No agreement exists as to the use of fine-needle aspiration to detect infection of necrosis. Ten of 23 clinical units completely abstain from needle aspiration; some use it, if clinical signs of infection persist, to obtain material for antimicrobial testing while others perform fine-needle aspiration routinely every other day for the same purpose. No consensus was achieved over the indication for haemofiltration to remove toxic metabolites in the absence of renal insufficiency. Seven of 23 units would use haemofiltration in this situation, while the other 16 would reserve it until required to correct volume overload. The indication for operative treatment is demonstration of infected necrosis *and* progressive organ failure for most units (14 of 23) while six would resort to operative treatment of infected necrosis or abscess before multiple organ failure develops. Three units would indicate operative revision if the patient did not respond to conservative therapy, even if abscess formation or infection of necrosis could not be demonstrated. Routine computed tomography to monitor the course of pancreatitis is used by ten of 23 units, while the majority calls for a more discriminate use based on clinical criteria. Regarding the high mortality rate associated with acute necrotizing pancreatitis, the questionnaire asked about the use of prognostic scores in the addressee's units. Eleven units apply prognostic scores (Acute Physiology And Chronic Health Evaluation II/III in six units), but no information was given about how scores affected patient management in these units.

Cost-effectiveness of hand-sewn *versus* stapled anastomoses

Many prospective randomized and controlled trials have compared traditional hand suture with stapling techniques for gastrointestinal anastomoses at virtually every anastomotic site. In most instances the main study endpoints were leak rates or other postoperative complications. Cost-effectiveness, although not entirely neglected, has rarely been selected as a major study endpoint. Responding to increasing demands for cost-effective treatment, in April 1993 a group from Hamburg-Eppendorf initiated a randomized trial which compared the cost of stapled and hand-sutured anastomoses in the gastrointestinal tract until the end of 1995 (33 months)[5]. All patients in whom either anastomotic technique appeared feasible at the end of resection were eligible. Patients with inflammatory bowel disease (e.g. Crohn's disease) and those who underwent non-curative tumour operations or simple small bowel resections were excluded. All patients received antibiotic treatment of metronidazole combined with a cephalosporin from induction of anaesthesia until the third day after operation. Planned colonic resections required preoperative colonic lavage. Hand-sutured anastomoses were carried out as single-layer, interrupted sutures using both monofilament and braided absorbable suture material or monofilament non-absorbable sutures. End-to-end anastomoses were constructed mainly although side-to-side anastomoses were allowed where appropriate. Cost analysis included the cost of materials used plus the cost of operating room time. To determine efficiency, time to full enteral nutrition, anastomotic leak and stenosis rates, rate of other postoperative complications and length of hospital stay were analysed.

One hundred patients were randomized to each group, 80 women of median age 60 (range 25–90) years and 120 men aged 58 (range 21–87) years. Mean operative times were longer for hand-sutured than stapled anastomoses: 14 *versus* 8 min for small bowel, 17 *versus* 10 min for colon and 33 *versus* 23 min for rectal anastomoses. The cost of operating room personnel was calculated as 407 Deutschmarks (DM) per h (one senior surgeon, one fully qualified surgeon, one surgeon in training, one anaesthetist, one student and three nurses). Because the cost of the materials required for stapled anastomoses was much higher than that for hand-sutured anastomoses the total cost of the stapled anastomoses was higher: 1130 *versus* 350 DM for oesophagojejunostomy, 400 *versus* 206 DM for small bowel, 640 *versus* 240 DM for colonic and 1034 *versus* 389 DM for rectal anastomoses. This cost advantage for hand-sutured anastomoses was also apparent when the total cost of the operation was considered: gastrectomy, 2769 DM (stapled) *versus* 2087 DM (hand-sutured); distal gastrectomy, 2244 *versus* 1607 DM; Whipple's operation, 2868 *versus* 2614 DM; colonic resection, 1799 *versus* 1469 DM; and low anterior resection, 2665 *versus* 1620 DM. No significant differences were recorded when anastomotic leak rates (1 *versus* 2 per cent for stapled *versus* hand-sutured anastomoses) or the rate of stenoses (2 per cent in each group) were considered. Time to full enteral feeding was longer in the stapled group after ileocolostomy and in the hand-sutured group after Whipple's operation, but these differences did not give rise to a longer overall postoperative hospital stay in any of the operative groups. Indeed, hospital stay after Whipple's operation was 12 days after hand-suturing ($n = 12$) and 16 days after stapling ($n = 18$). The authors concluded that stapled anastomoses are not efficient and should be reserved for individual indications.

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Illustrations in colour

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Editorial Team of the BJS

Prospective randomized comparison between pylorus-preserving and standard pancreaticoduodenectomy

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Background: Pancreaticoduodenectomy, with either gastrectomy (Whipple procedure) or pylorus-preserving pancreaticoduodenectomy (PPPD), is a complex procedure. Technical diversity, variation and sampling bias exist among surgeons. Previous reports comparing these two procedures are retrospective and not randomized. These factors should be considered seriously and eliminated in comparisons between the two procedures.

Methods: From August 1994 to August 1997, a prospective randomized comparison was conducted between the Whipple procedure and PPPD performed by the same surgeon with the same approach and same anastomotic fashion for periampullary cancer. After exclusion of seven patients, 31 patients were eligible for the study, 16 receiving PPPD and 15 a Whipple procedure. No significant difference in the age, sex distribution, tumour localization or staging was noted between the two groups.

Results: One operative death after PPPD and no operative death after the Whipple procedure resulted in a 3 per cent mortality rate in the 31 patients. Median duration of the Whipple operation was 235 (range 195–305) min, with a median blood loss of 500 (range 230–3100) ml and a median blood transfusion of 0 (range 0–10) units. In the patients who had PPPD, median operating time was 230 (range 170–275) min, median blood loss was 350 (range 100–1200) ml and median blood transfusion was 0 (range 0–4) units. There were two minor leaks from the pancreaticojejunostomy after the Whipple procedure and no leakage after PPPD, resulting in 6 per cent minor leakage in 31 patients. These outcomes were not significantly different. Delayed gastric emptying was observed more frequently after PPPD (six of 16 patients) than after the Whipple procedure (one of 15 patients), with marginal significance ($P = 0.08$, two-sided Fisher's exact test).

Conclusion: In this prospective randomized study, both PPPD and the Whipple procedure were associated with low mortality and operative morbidity rates. There was no significant difference between PPPD and Whipple resection in terms of operative mortality and morbidity, operating time, blood loss and blood transfusion. PPPD was associated with more frequent delayed gastric emptying, although study of more patients is needed to confirm this.

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Introduction

In 1935, Whipple *et al.*[1] described a two-stage pancreaticoduodenectomy for the treatment of carcinoma of the ampulla of Vater. In the report, the distal stomach, pylorus and proximal duodenum were preserved. In 1941, however, Whipple[2] reported the first successful one-stage radical pancreaticoduodenectomy in which the distal stomach, pylorus and duodenum were removed. Since then, a number of technical modifications have been reported for the treatment of periampullary malignant diseases. Watson[3] described the first pylorus-preserving pancreaticoduodenectomy (PPPD) in 1944; he preserved the whole stomach and 2·5 cm of duodenum, restoring the gastrointestinal continuity by duodenojejunostomy. This technique was not applied widely, however, until Traverso and Longmire[4] employed PPPD in two patients in 1978, in order to reduce the postgastrectomy syndrome following Whipple resection and to maintain better functional results. In recent years, PPPD has been used increasingly in patients with periampullary tumours or carcinoma of the head of the pancreas[5–8].

The operative mortality rate of pancreaticoduodenectomy has decreased recently[9–11], even approaching zero in some series[12–15], but the operative morbidity rate remains high, occasionally approaching 40–50 per cent[9–11], most often including intra-abdominal abscess, sepsis, pancreatic fistula and delayed gastric emptying[7–11,16–18]. Some reports have compared these two procedures with respect to morbidity, mortality, long-term complications and survival[19–23], but they were not prospective randomized studies. Furthermore, pancreaticoduodenectomy, whether with gastrectomy (Whipple operation) or PPPD, is a complex procedure. Great diversity and technical variation exist among surgeons, even in the same institution. Any comparison between these two procedures seems inappropriate unless the technical diversity and variation are kept to a minimum. Accordingly, a prospective randomized study was conducted to compare the operative complications between the Whipple procedure and PPPD done by a single surgeon with the same technique, same approach and same anastomotic fashion for a similar group of patients with periampullary and pancreatic malignancy.

Table 1 Characteristics of patients according to treatment

	Whipple (*n* = 15)	PPPD (*n* = 16)
Sex ratio (M : F)	11 : 4	7 : 9
Mean (range) age (years)	59 (41–76)	60 (43–77)
Age ≥ 65 years	6	6
Localization		
Head	3	2
Periampullary	12	14
Stage		
I	3	2
II	4	5
III	5	5
IV	3	4

PPPD, pylorus-preserving pancreaticoduodenectomy

Patients and methods

From August 1994 to August 1997, 45 patients underwent pancreaticoduodenectomy for various diseases. Of these patients, three had gastric cancer, one had benign duodenal leiomyoma and three had chronic pancreatitis, and were excluded from the study. The remaining 38 patients had either pancreatic head cancer or periampullary carcinoma. They were randomized prospectively to receive either a Whipple procedure or PPPD. Five patients initially randomized to PPPD were converted to a Whipple procedure, and were excluded because of very extensive involvement (two patients), ischaemic change at the duodenal end after dissection (one), previous exploration at another hospital for a misdiagnosis of common bile duct stone 1 week before operation (one) and chronic duodenal ulcer with severe scar formation which made safe duodenal dissection impossible (one). Two patients initially randomized to the Whipple procedure were excluded from the study, one because of a concomitant right hepatic lobectomy for a concurrent hepatic mass, and the other because of a concomitant superior mesenteric vein resection. There were finally 31 patients eligible for the study; 16 underwent PPPD and 15 the Whipple procedure. There were no significant differences in the age, sex distribution, tumour localization and staging between patients having Whipple resection and those having PPPD (*Table 1*).

Percutaneous transhepatic biliary drainage or endoscopic nasobiliary drainage was used routinely to relieve the obstructive jaundice before operation if the bilirubin level was higher than 10 mg/dl. Twenty-six patients received preoperative biliary decompression. All operative procedures were performed by the same surgeon (P.-W.L.) with the same technique, same approach and same anastomotic fashion[15]. In the Whipple pancreaticoduodenectomy, the vagus nerves were preserved and the distal two-thirds of the stomach was transected. In PPPD, the right gastric artery was preserved, unless the artery restricted the mobility of the stomach. The duodenum was dissected and divided at least 2 cm distal to the pylorus. Reconstruction was accomplished by single-layer end-to-side hepaticojejunostomy without T tube drainage, end-to-side pancreaticojejunostomy with an appropriate paediatric nasogastric tube as a temporary stent for 3 weeks and gastrojejunostomy or single-layer duodenojejunostomy. Only one jejunal loop was used for reconstruction (*Fig. 1*). No somatostatin or analogue was used in these patients.

Statistical analysis

Continuous data (operating time, blood loss and blood transfusion) were compared between the Whipple and PPPD groups using Student's *t* test, and the incidence of delayed gastric emptying and other categorical data were compared with Fisher's exact test. Delayed gastric emptying was defined as occurring when the nasogastric tube was left in place for 10 days or more plus one of the following: (a) emesis after removal of the nasogastric tube, (b) reinsertion of a nasogastric tube or (c) failure to progress with diet[25].

Results

There was one postoperative death in the 16 patients having PPPD, and none following the Whipple procedure, resulting in a 3 per cent mortality rate in the 31 patients. The death occurred in a 56-year-old woman who had had a modified radical mastectomy for cancer of the

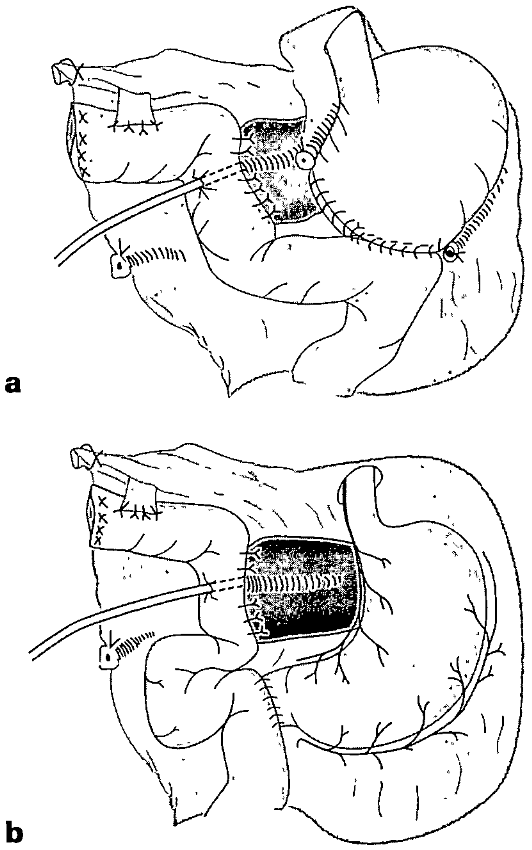

Fig. 1 Reconstruction after pancreaticoduodenectomy: **a** standard Whipple procedure; **b** pylorus-preserving pancreaticoduodenectomy

left breast with axillary lymph node involvement 1 year before this admission. After PPPD she developed intra-abdominal abscess with sepsis and delayed gastric emptying. No definite evidence of leakage of the pancreaticojejunostomy was observed. The patient died 40 days after operation from sepsis and multiple organ failure.

Table 2 shows operating time, blood loss and blood transfusion for the two groups. Differences in these parameters were not significant.

Table 3 shows the postoperative complications. Two minor leaks were seen from the pancreaticojejunostomy following the Whipple procedure but no leak after PPPD, resulting in a 6 per cent minor leakage rate in the 31 patients. The leaks did not result in gastric emptying delay and they healed spontaneously after conservative treatment. No leak was observed at the hepaticojejunostomy in either group.

A temporary clinically evident delay in gastric emptying was observed in one of the 15 patients having the Whipple operation and in six of the 16 having PPPD, a difference that was marginally significant ($P = 0{\cdot}08$, two-sided Fisher's exact test). The longest delay in gastric emptying after PPPD was 51 days; the only gastric emptying delay after the Whipple procedure involved postoperative pancreatitis, and the delay resolved on day 26 after operation. Postoperative pancreatitis affected one patient after PPPD, and also resulted in delayed gastric emptying; the delay resolved on the 15th postoperative day. Superficial wound infection was observed in one patient in each group.

Table 2 Operating time, blood loss and blood transfusion

	Whipple ($n = 15$)	PPPD ($n = 16$)	P	t
Operating time (min)				
Mean(s.d.)	237(30)	215(31)	< 0·1	1·975
Median (range)	235 (195–305)	230 (170–275)		
Blood loss (ml)				
Mean(s.d.)	687(670)	451(362)	> 0·2	1·20
Median (range)	500 (230–3100)	350 (100–1200)		
Blood transfusion (units)				
Mean(s.d.)	1·6(2·6)	1·0(1·4)	> 0·2	0·986
Median	0 (0–10)	0 (0–4)		

PPPD, pylorus-preserving pancreaticoduodenectomy

Table 3 Complications after operation

	Whipple ($n = 15$)	PPPD ($n = 16$)
Death	0	1
Minor pancreatic leakage	2	0
Biliary leakage	0	0
Delayed gastric emptying	1	6*
Pancreatitis	1	1
Wound infection	1	1
Cardiovascular accident	1	0
Upper gastrointestinal bleeding	1	0

PPPD, pylorus-preserving pancreaticoduodenectomy. *$P = 0{\cdot}08$ (Fisher's exact test), there were no significant differences

Table 4 Status of the pancreatic remnant, pancreatic duct and common bile duct after pancreaticoduodenal resection

	Whipple ($n = 15$)	PPPD ($n = 16$)
Pancreatic duct (mm)		
Mean (range)	3 (1–8)	3 (1–8)
> 4 mm	6	7
Pancreatic remnant		
Soft	10	12
Fibrotic	5	4
Bile duct (mm)		
Mean (range)	14 (5–35)	15 (9–35)

PPPD, pylorus-preserving pancreaticoduodenectomy. There were no significant differences

The status of the pancreatic remnant, pancreatic duct and common bile duct after pancreaticoduodenal resection between two groups was not different (*Table 4*). Because there were only two minor leaks at the pancreaticojejunal anastomosis in the 31 patients, the relationship between leakage and the status of the pancreatic remnant and the pancreatic duct could not be determined.

Discussion

Previous reports have discussed the comparison between the Whipple procedure and PPPD; however, they were retrospective and the choice of operation was according to the surgeon's preference[19–24]. Sampling bias and technical variation were unavoidable problems in these reports. To the authors' knowledge, the present study is the first prospective randomized report comparing the complications of PPPD and Whipple resection. All the procedures were performed by one surgeon using the same technique, same approach and same anastomotic fashion.

Although the operative mortality rate for pancreaticoduodenectomy has decreased, the morbidity rate remains high[7–15]. There was one death in these 31 patients, comparable with other reports[7–15]. Klinkenbijl *et al.*[20] in their retrospective report stated that PPPD was an easier and less time-consuming operation with less blood loss compared with the Whipple procedure. However, in the present prospective randomized study, there was no significant difference between the Whipple operation and PPPD in term of operating time, blood loss and blood transfusion. Sampling bias and technical diversity and variation were important variables in their report[20]. Although the extent of resection is greater for a Whipple procedure than for PPPD, the dissection for the duodenal end is more delicate in PPPD than in the Whipple procedure. When the operative surgeon gains more experience, the difference in term of operating time, blood loss and blood transfusion between the Whipple operation and PPPD becomes less significant.

Leakage from the pancreaticojejunostomy after pancreaticoduodenectomy is a frequent and major complication[16,17]. No significant difference in leakage rate at the pancreaticojejunostomy between PPPD and Whipple resection was noted[16,17]. Status of the pancreatic remnant, diameter of the pancreatic duct, intraoperative blood loss, technique and fashion of the anastomosis, and experience and skill of the surgeon may all contribute to leakage[9–11]. Because there were only two minor leaks in 31 patients, the relationship to these factors could not be defined. However, experience and the technical ability of the surgeon are important for the success of the pancreaticojejunostomy following pancreaticoduodenectomy.

Conflicting results with regard to postoperative delayed gastric emptying after the Whipple procedure or PPPD have been reported[18–24]. In the present series, the incidence of delayed gastric emptying in the PPPD group (six of 16 patients) was higher than that in the Whipple group (one of 15), although this difference was only marginally significant ($P = 0{\cdot}08$, Fisher's exact test). The study was highly suggestive of a drawback of PPPD, although more patients are needed to reach a more definite conclusion. The statistical power of the study to detect a significant difference between the two groups was only 60 per cent. Great care was taken of the blood supply to the duodenum during PPPD, and one PPPD was converted to a Whipple procedure because of potential ischaemia, so it is unlikely that ischaemia was a major factor contributing to the gastric emptying delay in the present series. Anatomical position, as proposed by Ueno *et al.*[26], was not a major concern for delayed gastric emptying in this study. Leakage at the pancreaticojejunostomy, intraoperative blood loss, transfusion and operating time did not account for the difference in gastric emptying delay between PPPD and the Whipple procedure in this prospective study. Postoperative pancreatitis might be one of the reasons for gastric emptying delay. Both patients, including the only patient who had postoperative pancreatitis in the Whipple group, developed delayed gastric emptying. Postoperative pancreatitis was observed at a similar rate to that reported by others (2 per cent)[7], but most patients with delayed gastric emptying after PPPD did not have pancreatitis. The real mechanism for delayed gastric emptying after pancreaticoduodenectomy needs further investigation.

In conclusion, in this prospective randomized study both PPPD and the Whipple procedure were associated with a low mortality rate and few major operative complications. There was no significant difference between PPPD and the Whipple operation in terms of operating time, blood loss and blood transfusion. PPPD was associated with more frequent delayed gastric emptying, although more patients are needed to demonstrate this conclusively.

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Original article

Randomized clinical trial of ultrasonic dissector or conventional division in distal pancreatectomy for non-fibrotic pancreas

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Background: Resection of the non-fibrotic pancreas is prone to postoperative pancreatic fistula because of well preserved exocrine secretions and easily crushed soft parenchyma. The purpose of this study was to evaluate ultrasonic dissection for division of the non-fibrotic pancreas in distal pancreatectomy.
Methods: All pancreata included in this study were soft on direct palpation and their main ducts had no dilatation, at least proximally from the transection line. Fifty-eight patients with gastric cancer or pancreatic disease were randomly assigned to the two groups. In the ultrasonic dissection (UD) group ($n = 27$), all pancreatic ducts were identified and ligated securely. The stump was left open without parenchymal suturing. In the conventional (CV) group ($n = 31$), the pancreas was cut with a knife and the stump was oversewn in mattress fashion. The main pancreatic duct was ligated in all patients in both groups. Pancreatic fistula was defined as a pancreatic fluid discharge for more than 7 days after operation diagnosed according to amylase concentration in the drainage fluid.
Results: In the UD group, approximately 20–30 tubes including a mean(s.d.) 5·2(0·8) (range 4–6) pancreatic ducts were skeletonized and ligated per patient. There were nine pancreatic fistulas (16 per cent); one in the UD group and eight in the CV group ($P = 0.020$).
Conclusion: In distal pancreatectomy for the non-fibrotic pancreas, ultrasonic dissection without suture closure of the stump reduced the incidence of pancreatic fistula compared with conventional division and suture, in this randomized trial.

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Introduction

Pancreatic fistula is the most common complication following distal pancreatectomy[1–4]. The soft non-fibrotic pancreas is, in particular, associated with a high incidence because of well preserved exocrine function and easily crushed soft parenchyma. With main pancreatic duct ligation, major leakage of pancreatic juice rarely occurs, but even small pancreatic secretions can lead to abscess formation, subsequent sepsis, and haemorrhage[1,2]. Main duct ligation and subsequent suture closure of the pancreatic stump has been the standard management of the cut surface. Recently, distal pancreatic closure with a stapler was advocated to be a simple and safe technique[5]. However, these techniques do not occlude small duct branches with absolute certainty and cause additional parenchymal trauma, in particular in the soft non-fibrotic pancreas.

In an attempt to reduce the pancreatic fistula rate, a new technique of distal pancreatectomy using an ultrasonic dissector (CUSA System; Cooper Medical Devices, Mountainview, California, USA) has been devised; results for seven initial cases have been published[6]. In this article, ultrasonic dissection of non-fibrotic pancreas was evaluated in a prospective randomized clinical study.

Patients and methods

Patients

Between July 1994 and August 1998, 58 patients with a non-fibrotic pancreas underwent distal pancreatectomy. Patient demographics are summarized in *Table 1*. In 50 patients with gastric cancer and one with gastric MALT (mucosa-associated lymphoid tissue) lymphoma, total

Table 1 Patient demographics

	Ultrasonic dissection	Conventional
No of patients	27	31
Age (years)*	57·7(10·9) (28–74)	58·5(11·9) (41–83)
Sex ratio (M : F)	18 : 9	18 : 13
Albumin (g/dl)*	3·6(0·5)	3·5(0·4)
Total cholesterol (mg/dl)*	170·2(36·2)	164·4(20·1)
Preoperative morbidity	2	3
Indication for distal pancreatectomy		
Gastric tumour	24	27
Stage I and II	11	12
Stage III and IV	13	15
Pancreatic disease	3	4

*Values are mean(s.d.) (range)

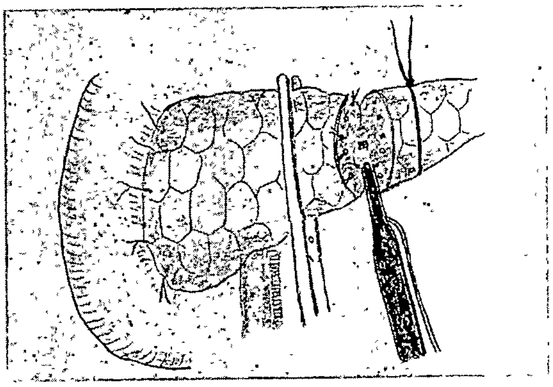

Fig. 1 Schematic drawing of distal pancreatectomy using an ultrasonic dissector

gastrectomy was performed with distal pancreatectomy to resect lymph nodes or tumour invasion to the pancreas. Seven patients had distal pancreatectomy for pancreatic disease. The gland consistency, at least in the proximal pancreas, was normal on palpation in all cases, and none of the main pancreatic ducts on the cut surface was dilated (less than 3 mm in diameter).

The 58 patients were randomly assigned to the ultrasonic dissection (UD) group ($n = 27$) or the conventional surgery (CV) group ($n = 31$) by drawing lots. The study was approved by the local ethics committee. Informed consent was obtained from all participants. The UV group included 24 patients with gastric cancer and three with pancreatic disease (two pancreatic cancers and one pseudocyst), while the CV group consisted of 27 patients with gastric cancer, one with MALT lymphoma and four with pancreatic disease (one pancreatic cancer, one solid cystic tumour, one pseudocyst and one serous cystadenoma). The two groups were well matched with regard to age, sex, type of underlying disease, cancer stage, results of preoperative nutritional assessment and preoperative morbidity (liver cirrhosis and diabetes mellitus). Stage grouping of gastric cancer was carried out according to the clinical classification published by the Japanese Research Society for Gastric Cancer[7].

Surgical procedures

After dissecting the spleen and the distal pancreas from the retroperitoneum, the splenic artery and vein were ligated and divided proximal to the plane of pancreatic dissection. The pancreas was clamped with intestinal forceps proximally and ligated distally to the plane of dissection to prevent bleeding into the operative field.

Subsequent procedures in the UD group have been described previously[6]. Briefly, the pancreas was transected by the ultrasonic dissector at the lowest vibration level. During the transection procedure, even small pancreatic ducts and vessels were adequately exposed, tied proximally with 4/0 silk sutures and divided. The stump was left open without parenchymal suturing (*Fig. 1*). In the CV group, the pancreas was transected using a knife and the main pancreatic duct was ligated with 3/0 silk. The cut edge of the proximal pancreas was oversewn with interrupted mattress sutures of 3/0 polypropylene.

A soft rubber sheet drain was placed near the pancreatic stump as a closed drain. The drain was removed when the volume was less than 50 ml/day and the amylase concentration was less than three times that in the serum.

Histological analysis

All ligated specimens on the cut surface of the pancreas were fixed in 10 per cent buffered formalin, embedded in paraffin by automatic tissue processing, and stained with haematoxylin and eosin in five specimens in the UD group. Pancreatic ducts were identified and counted microscopically.

Diagnosis of pancreatic fistula

Postoperative pancreatic fistula was defined as an external discharge of pancreatic fluid for more than 7 days after operation, with an amylase concentration of more than three times the serum concentration.

Statistical analysis

Results were expressed as mean(s.d.). Statistical analysis was by χ^2 test for comparison of postoperative pancreatic fistula rates between the UD and CV groups. Differences were considered significant at $P < 0·05$.

Results

In the UD group, approximately 20–30 tubes including the pancreatic ducts and small blood vessels were skeletonized and ligated per patient. Among them, 5·2(0·8) (range 4–6) pancreatic ducts, including the main duct, were identified microscopically in each of the five pancreatic stumps examined.

Time required for division of the pancreas was 23·0(2·8) (range 20–28) and 9·1(4·8) (range 12–28) min in the UD and the CV groups respectively ($P = 0.039$).

Pancreatic fistulas developed in nine patients (16 per cent) in this series, one in the UD group and eight in the CV group ($P = 0.020$). Two pancreatic fistulas in the CV group were complicated by an intraperitoneal abscess around the pancreatic stump. They were treated successfully by percutaneous drainage, irrigation, and/or simultaneous administration of antibiotics, protease inhibitor and somatostatin analogue (octreotide). No other patient had an infectious complication. Mean drainage time until closure of the pancreatic fistula was 43·4(16·9) (range 20–77) days in the CV group and 21 days in the UD group. No patient with pancreatic fistula died. None of the seven patients with pancreatic disease had a postoperative pancreatic fistula. All fistulas occurred in patients with gastric cancer.

Discussion

Distal pancreatectomy for the non-fibrotic pancreas is associated with a high pancreatic fistula rate. Randomized controlled studies carried out recently demonstrated the efficacy of octreotide in reducing the frequency of pancreatic fistula after pancreatic surgery[3,8]. Intraoperative preventive measures are still important for further reduction of pancreatic fistula rates and better outcomes following distal pancreatectomy.

Several intraoperative measures against pancreatic fistula have been reported. Konishi *et al.*[9] described segmental occlusion of the pancreatic duct with prolamine after distal pancreatectomy. Moriura *et al.*[10] reported closure of the pancreatic stump with a gastric or jejunal seromuscular flap. The present authors previously reported the prophylactic effect of fibrin glue sealing for management of the pancreatic stump[11]. Use of the ultrasonic dissector seems to be a simpler and more inexpensive method, and could be combined with other prophylactic methods, such as fibrin glue sealing or/and octreotide administration.

The present findings supported the theoretical advantages of ultrasonic dissection for distal pancreatectomy. First, smaller pancreatic ducts as well as the main duct on the cut surface were skeletonized, identified certainly and ligated securely. Second, because a dry pancreatic stump can be obtained immediately after resection, subsequent suture closure of the stump, which may cause internal laceration and ischaemic damage of the parenchyma, can be avoided. In addition, the ultrasonic dissector has no detrimental effect. The additional time required to use the ultrasonic dissector is negligible.

In the literature, incidences of pancreatic fistula of between 9·8 and 26·8 per cent have been reported after distal pancreatectomy[1–4]. The incidence in the present control group (26 per cent; eight of 31) was rather high compared with values reported by others. However, most articles on distal pancreatectomy and its complications included considerable percentages of patients with benign pancreatic diseases, mostly chronic pancreatitis, or trauma[2–5]. Over 90 per cent of patients (53 of 58) included in this study were suffering from malignant disease. Furthermore, the stumps and remainders of the pancreata all had a normal consistency in this series. Hamanaka *et al.*[12] recently reported that patients with pancreatic parenchyma of a normal consistency produced more pancreatic juice and had a higher rate of pancreatic leakage. Different diagnostic criteria also affect the pancreatic fistula rate. Cogbill *et al.*[2] and others[13,14] defined a pancreatic fistula as drainage of more than 50 ml of amylase-rich fluid (greater than three or five times the normal plasma level). The definition of amylase-rich fluid regardless of drainage volume was used in the present study, in order to detect even smaller pancreatic fistulas.

In conclusion, in distal pancreatectomy with a non-fibrotic pancreas, which carries a high risk for postoperative pancreatic fistula, ultrasonic dissection without suture closure of pancreatic stump significantly reduced the incidence of pancreatic fistula. This technique is simple and inexpensive, and can be combined with other prophylactic measures against pancreatic fistula following distal pancreatectomy.

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Short note

Randomized trial of open *versus* closed day-case haemorrhoidectomy

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Introduction

Full three-quadrant haemorrhoidectomy can be performed as a day-case procedure with high patient satisfaction, a low readmission rate and few complications[1]. Haemorrhoidectomy is most commonly performed open (using either scissors dissection or diathermy) or closed. Proponents of the latter have suggested that primary closure of the wounds results in less pain after operation[2]; however, this claim has not been substantiated in surveys[3]. Similarly, prospective studies have shown no differences between the open and closed techniques[4]. The influence of operative technique on postoperative pain has not been addressed in the setting of day-case haemorrhoidectomy.

Patients and methods

Consecutive patients were recruited. As with open haemorrhoidectomy, the closed technique was carried out using diathermy dissection[5] and the wounds were sutured with plain catgut. Patients received local anaesthetic infiltration and a diclofenac suppository. They were discharged home with non-opiate analgesia, metronidazole, lactulose and topical glyceryl trinitrate[1].

Postoperative pain was assessed using a linear analogue scale. Patient satisfaction was determined using a questionnaire, scoring between –3 (extreme dissatisfaction with day surgery) and +3 (complete satisfaction).

Analysis of variance was used to compare mean pain scores between groups and between days. The Mann–Whitney *U* test was used for categorical data. It was calculated that a sample size of 18 was necessary to show a significant difference at the 5 per cent level with 80 per cent power.

Results

Seventeen patients underwent open and 18 closed haemorrhoidectomy (*Table 1*). The first postoperative bowel motion was within 24 h of surgery for 22 patients, with no difference between the groups ($P = 0·69$). There was no significant difference in mean pain scores between the groups ($P = 0·33$). Twelve patients having open haemorrhoidectomy and 11 in the closed group used additional analgesia ($P = 0·72$).

There were no readmissions and no major complications. Ten patients with closed haemorrhoidectomy had wound dehiscence. This did not delay healing at 6 weeks, which was complete in all 18 patients, compared with 16 of 17 after open haemorrhoidectomy ($P = 0·49$, Fisher's exact test).

Overall 30 patients expressed a preference for day surgery, while the remaining five were indifferent. The satisfaction score was similar at week 1 ($P = 0·75$) and week 6 ($P = 0·26$). Postoperative return to normal activity was also similar for the open (median 15 (range 6–25) days) and closed (18 (7–25) days) groups ($P = 0·33$).

Discussion

This prospective randomized trial has shown no differences in postoperative pain, wound healing, return to normal activities or patient satisfaction between closed

Table 1 Patient characteristics and extent of surgery in the two groups

Operative technique	No. of patients	Age (years)*	Sex ratio (M : F)	Anxiety score†	Depression score†	No. of piles excised		
						≥3	2	1
Open	17	44 (27–68)	7 . 10	7·5(4)	4·5(2·5)	14	3	0
Closed	18	46 (36–75)	10 . 8	8(4)	5(3·5)	13	4	1

Values are *mean (range) or †mean(s.d.)

and open haemorrhoidectomy techniques in the day-case setting. It has confirmed that day-case haemorrhoidectomy is feasible for all patients irrespective of the extent of haemorrhoids, as long as a carefully designed perioperative care package is employed[1]. Postoperative pain is manageable with minor oral analgesia, thus avoiding opiates and associated problems. Complications are few; there is a high level of patient satisfaction and early return to normal activities. An open diathermy technique or a closed technique may be used according to the individual surgeon's preference, with no demonstrable advantage of one over the other.

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Randomized trial to study the effect of fundic mobilization on long-term results of Nissen fundoplication

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Background: It has been suggested that fundic mobilization in Nissen fundoplication decreases adverse postoperative symptoms and increases the durability of the fundic wrap. There are no previous randomized, prospection long-term studies assessing this. This study addresses the question.

Methods: Fifty consecutive patients were randomized to undergo open Nissen–Rossetti fundoplication with total fundic mobilization ($n = 26$) or an identical procedure without mobilization ($n = 24$). After a median of 36 (range 6–53) months 49 had endoscopy and a personal interview.

Results: Oesophagitis was cured in 20 of 21 patients who had fundic mobilization and 18 of 19 who did not. A defective fundic wrap was observed in five and recurrent reflux symptoms in six of those who had fundic mobilization compared with two and one respectively of those who did not (P not significant). Recurrent sliding hiatal hernia was observed in nine of those with a mobilized fundus and one of those without ($P = 0{\cdot}02$). There was no significant difference in incidence of new-onset long-term dysphagia, subjective belching ability, amount of flatus or bloating between the study groups.

Conclusion: Fundic mobilization did not give any apparent advantage regarding postoperative adverse effects. Instead, it was associated with a higher rate of recurrent hiatal hernia.

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Introduction

Nissen fundoplication gives good cure of symptoms of gastro-oesophageal reflux and heals oesophagitis effectively[1,2]. The main determinant of the outcome is the state of the fundic wrap[1,3]. Adverse effects, including dysphagia, increased flatus and bloating, and disturbed ability to belch and vomit have also been described[4,5]. Some authors have advocated rejection of total fundoplication in favour of partial wrapping techniques to overcome these difficulties[6–8]. To decrease these postoperative symptoms and also to increase the durability of the wrap, total fundoplication has been modified: a floppy fundoplication with mobilization of the fundus, with a large-bore dilatator within the oesophagus during plication, has been suggested[9–11]. There are only two previous prospective randomized studies assessing the effects of fundic mobilization on postoperative dysphagia after open[12] or laparoscopic[13] fundoplication; no advantage of mobilization could be shown. The follow-up time in these studies was, however, only 6 months. Fundic mobilization does not diminish flatus or bloating after open surgery[14]. There have not been any studies with longer follow-up.

Controversy also exists regarding the need for repair of the hiatus when performing fundoplication[10,15,16]. Few cases of postoperative paraoesophageal hernia have been reported after open surgery[1,17], but the greater frequency after laparoscopic fundoplication[18] emphasizes the issue especially with the increasing numbers of fundoplications performed during the era of laparoscopic antireflux surgery[19].

The aim of the present study was to evaluate the effects of fundic mobilization on clinical long-term results of open Nissen fundoplication.

Patients and methods

Fifty-two consecutive patients with confirmed gastro-oesophageal reflux disease were referred for antireflux surgery during the period 1991–1993. Fifty patients (two declined) were randomized to have either a conventional

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open Nissen–Rossetti[15] anterior wall 360° fundoplication without fundic mobilization ($n = 24$) or to have the floppy procedure with full mobilization of the fundus by division of the gastrophrenic and gastrosplenic ligaments and ligation of all the short gastric vessels ($n = 26$)[11]. Randomization was done by opening a sealed envelope containing one of an equal number of sheets labelled either for floppy or conventional technique. Except for fundic mobilization, the operations were identical. The hiatus was not repaired routinely. This was done in only one patient with a large hiatus hernia[11,15,16]. The 1·5–2-cm long fundic wrap was constructed with three or four strong non-absorbable sutures, permitting one or two of the surgeon's fingers to be placed beneath the wrap without any tightness while a 32-Fr gastric tube was in the oesophagus. The wrap was not sutured to the oesophagus, but instead was anchored with the bottom stitch to the gastric side of the gastro-oesophageal junction. All operations were performed by the authors. The hospital ethics committee approved the study protocol, and informed consent was obtained from all patients.

Preoperative endoscopy[20] and oesophageal 24-h pH recording[21] were done in all patients. After a median of 36 (range 6–53) months, 49 of the 50 patients had a personal interview and endoscopy (by M.E.S.L.). One patient (without fundic mobilization) had died from coronary heart disease during the follow-up period. A standard formula was used in the preoperative and postoperative interview. During the interview, patients were encouraged to report any possible side-effects or recurrent/persistent symptoms, in order to reduce the bias because the operating surgeon was acting as an interviewer. The DeMeester and Johnson scale[22,23] was used to score clinical outcome of heartburn, regurgitation and dysphagia. Special attention was also directed to bloating and flatus; the patients were encouraged to report any subjective increase in symptoms of and disturbance from flatus and bloating. The ability to belch and vomit were graded as none, possible with some difficulties and restored to preoperative status[1]. The state of the fundic wrap was checked with a retroflexed endoscope[1,3,9]. Slipping was identified when there was a distinct gastric pouch above the narrowing caused by the folds of the wrap. Disruption of the wrap implied that no folds were visible; in cases of partial disruption, only distorted loose folds were seen at the oesophagogastric junction.

Short-term results of the first 25 patients have been reported previously[12,14]. Data are expressed as median (range). Non-parametric tests (contingency table with G^2-statistics, Wilcoxon signed rank test and Mann–Whitney *U* test) were used in the statistical assessment.

Results

Heartburn and regurgitation improved significantly in both groups ($P = 0{\cdot}0001$, Wilcoxon signed rank test). Before operation all patients had moderate to severe symptoms as measured by the DeMeester–Johnson clinical reflux score. At follow-up mild symptoms were reported by six who had fundic mobilization compared with one who did not ($P = 0{\cdot}054$, G^2-statistics).

The preoperative and postoperative incidence of dysphagia was similar in both groups (*Fig. 1*). New-onset dysphagia was observed in two patients after fundic mobilization compared with five of those without ($P = 0{\cdot}07$, G^2-statistics). All cases of new-onset dysphagia were mild and occasional. These patients did not need oesophageal dilatation, they ate normal solid food, and symptoms occurred only during ravenous eating. There were no differences between the groups in subjective ability to belch, amount of flatus or bloating (*Table 1*).

Two patients in each group had objectively observed recurrent reflux defined by pathological 24-h pH monitoring or endoscopic oesophagitis. The fundic wrap was defective in five of the 26 who had fundic mobilization and in two of the 23 who did not (*Table 2*). Objectively observed reflux and/or a defective wrap were observed in five patients with and three without fundic mobilization. Six of the seven patients with a defective wrap had objective and/or subjective findings of recurrent reflux. Four of the six patients with symptoms suggestive of reflux in the group with a mobilized fundus had a defective wrap, as did the only symptomatic patient in the other group.

Before operation a sliding hiatal hernia was observed in 21 of the 26 patients who had fundic mobilization and in

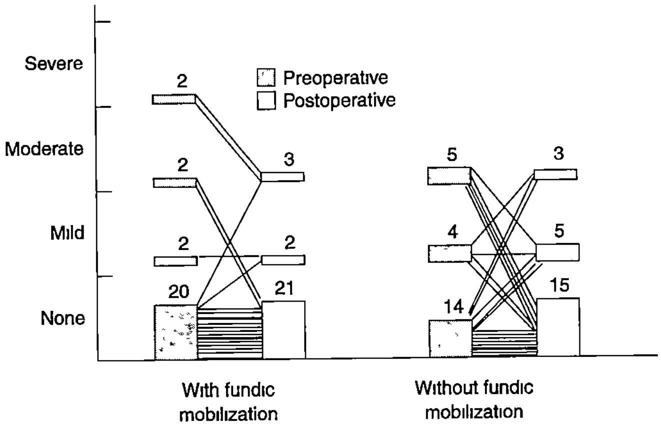

Fig. 1 Dysphagia in individual patients assessed by DeMeester–Johnson grades[22,23] a median of 36 months after Nissen fundoplication with or without fundic mobilization. There were no statistically significant differences

Table 1 Ability to belch and vomit, and increase in flatus and bloating a median of 36 months after fundoplication with or without fundic mobilization

	With mobilization (*n* = 26)	Without mobilization (*n* = 23)
Ability to belch		
None	4 (15)	6 (26)
With some difficulty	7 (27)	9 (39)
Restored to preoperative status	15 (58)	8 (35)
Unable to vomit	6 of 11	5 of 10
Flatus increased	11 (42)	10 (43)
Bloating increased	2 (8)	5 (22)
Flatus and/or bloating		
Increased	12 (46)	12 (52)
Occasionally disturbing	3 (12)	2 (9)

Values in parentheses are percentages. There were no statistically significant differences

Table 2 Fundic wrap and hiatus hernia at follow-up endoscopy a median of 36 months after fundoplication

	With mobilization (*n* = 26)	Without mobilization (*n* = 23)
Fundic wrap		
Intact	21 (81)	21 (91)
Disrupted	4 (15)†	1 (4)
Slipped	1 (4)	1 (4)
Sliding hiatal hernia*	9 (35)	1 (4)

Values in parentheses are percentages †All disruptions after mobilization of the fundus were partial; disruption of the wrap without mobilization was total. *P = 0 02 *versus* without mobilization

19 of the 24 patients who did not. A postoperative sliding hernia, i.e. intrathoracically displaced fundic wrap, was observed in ten patients (*Table 2*). Recurrent hernia was not associated with persistent or new-onset dysphagia, but rather with occurrence of disruption of the fundic wrap and thus with recurrent reflux symptoms. Sliding hernias were more common after fundoplication with fundic mobilization, even if patients with a defective wrap were excluded. An intrathoracic, but otherwise intact, wrap was not associated with symptoms of reflux. One complication occurred in conjunction with sliding postoperative hernia; a patient who had a mobilized fundus and an intrathoracic, but otherwise intact, wrap had a gastric ulcer at the lower border of the wrap. *Helicobacter pylori* was not found. The ulcer was cured by H_2-receptor antagonist therapy and did not recur during follow-up. The patient has, however, been taking a daily dose of ranitidine 150 mg.

Before operation 21 of the 26 patients who had fundic mobilization, and 19 of the 24 patients who did not had erosive oesophagitis. This was cured effectively in both groups. There were only two patients, one in each group, who had persistent acute erosions and fibrous scarring at follow-up endoscopy. Their fundic wraps were also defective.

Discussion

Operative techniques in this study were standardized; the authors performed all the operations and the only difference between the two groups was mobilization of the fundus. Cure of symptoms of reflux and healing of oesophagitis were equally effective, whether the fundus was mobilized or not, as long as the fundic wrap – the main determinant of the outcome[1,3] – remained intact. The cure rates in both groups were similar to those in previous reports on both open and laparoscopic antireflux surgery (*Table 3*). Fundic mobilization did not protect the wrap from disruption, as has been suggested previously[31].

Fundic mobilization increased the risk of recurrence of hiatal hernia, which was also reported by Lundell *et al.*[17]. Four of the ten recurrent hernias were associated with disruption of the fundic wrap, and four of the seven patients with a defective wrap had a hernia. Observations after paraoesophageal hernia repair suggest that wrap disruption may have a role in the development of recurrent hernia[32]. Herniation may also itself provoke disruption by stretching the wrap against the hiatal orifice. Nevertheless, the remaining six of the ten patients with hernia had an endoscopically intact wrap, and a mobilized fundus. Intrathoracic herniation of an intact fundic wrap was not associated with recurrent reflux or other symptoms, except in one patient with a gastric ulcer at the lower border of the wrap. Ulcers within the fundic wrap may lead to life-threatening complications[33–35]. Thus, it seems wise to avoid herniation and routinely to approximate the crura, especially if the fundus is mobilized. This may also reduce the rate of disruption of the wrap.

The frequency of persistent postoperative dysphagia varies greatly in previous studies, after both open and laparoscopic fundoplication, regardless of fundic mobilization (*Table 3*). This reflects differences in criteria used for dysphagia (scales range from bolus obstruction necessitating vomiting or endoscopy to occasionally increased awareness of food passage) and differences in methods of obtaining the data. The numbers in the present study are within this range. Preoperative dysphagia declined or disappeared in a great majority of the patients in both groups. One may wonder if there was significant dysphagia at all; many of the present patients with reflux described themselves as ravenous eaters, and if this habit continued after operation they would inevitably meet more resistance to food passage[36]. Dysphagia had clinical consequences in only two patients with oeso-

Table 3 Postoperative adverse effects after open or laparoscopic Nissen fundoplication, with or without fundic mobilization

Reference	Year	No. of patients	Follow-up (months)	Dysphagia (%)	Inability to belch (%)	Inability to vomit (%)	Bloating (%)	Flatus (%)
Open/wrap not mobilized								
Negre[5]	1983	60	120	43	—	—	—	—
Shirazi *et al.*[24]	1987	350	24–240	3	—	—	6	—
Ackermann *et al.*[25]	1988	268	180	38	22	45	50	30
Luostarinen *et al*[2]	1993	25	240	44	28	62	36	36
Luostarinen[1]	1993	109	77	43	17	40	27	67
Open/wrap mobilized								
Donahue *et al.*[9]	1985	62	49	0	2	—	2	—
DeMeester *et al.*[10]	1986	100	45	14	36	63	15	38
Stipa *et al.*[26]	1989	32	84	43	—	—	40	—
Lundell *et al*[17]	1996	65	60	10	20	85	25	30
Laparoscopic/wrap not mobilized								
Anvari and Allen[27]	1998	381	6	1	—	—	—	49
Watson *et al*[13]	1997	50	6	33	38	—	—	35
Laparoscopic/wrap mobilized								
Watson *et al.*[13]	1997	52	6	29	53	—	—	41
Dallemagne[28]	1993	118	3	17	—	—	5	—
Collard *et al.*[29]	1994	39	1	40	—	—	—	49
Hinder *et al.*[30]	1994	154	4–24	5	—	—	—	—

phageal stricture. In a prospective randomized study of mobilization of the gastric fundus or not, Watson *et al.*[13] found no difference in dysphagia 6 months after laparoscopic fundoplication. Similarly, in the present study, with median follow-up of 3 years, at 6–53 months there was no significant difference in new-onset dysphagia.

After fundoplication, inability to belch has been reported in 2–53 per cent of patients, whether or not the fundus was mobilized (*Table 3*). No clear difference in subjective ability to belch between the study groups was found in the present study or that of Watson *et al.*[13]. When assessing the significance of postoperative changes in belching ability, it must be taken into account that belching is actually gaseous reflux[37]. Thus, fundoplication probably inevitably reduces belching ability from the preoperative situation. The authors have previously used a radionuclide technique to assess objectively the effect of fundoplication on belching ability[14]; preoperative belching was found to be excessive compared with that in healthy controls. After the operation it was normalized rather than disturbed, regardless of fundic mobilization. Fundic mobilization did not have any effect on ability to vomit: about half of the present patients in both groups were unable to vomit. Flatus was increased in both groups, but was very seldom disturbing. Increased bloating was reported infrequently.

In conclusion, Nissen fundoplication with fundic mobilization gave no clear advantage regarding postoperative dysphagia, subjective belching ability, flatus production or bloating. The possibility of a type II error must, however, be borne in mind, because of the suboptimal sample size. Up to 80 patients in both study arms would have been needed to show a 20 per cent difference with 90 per cent power. Fundic mobilization did not give either better prevention against wrap disruption or recurrence of symptoms of reflux. On the contrary, the risk of recurrent hiatal hernia was increased.

Acknowledgements

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Original article

Follow-up of patients with a thin melanoma

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Background: The aim of this study was to determine the value of follow-up in two subgroups of patients with a thin melanoma less than 0·76 mm and 0·76–1·5 mm thick.
Methods: The study group comprised all patients presenting to the Cardiff Melanoma Clinic from its introduction in 1976 to the end of 1994. All patients attend follow-up according to a strict protocol, determined by the thickness of the original melanoma (less than 0·76 mm, annually; more than 0·76 mm, every 2 months for 2 years, 3 monthly for 2 years, 4 monthly for 1 year and then annually).
Results: In total there were 306 patients with a thin melanoma: 178 with a melanoma thinner than 0·76 mm (group 1) and 128 with a melanoma of 0·76–1·5 mm (group 2). The groups were well matched for age (mean 50·6 (range 8–87) *versus* 50·6 (range 19–89) years respectively) and length of follow-up (mean 88·6 (range 4–296) *versus* 80·4 (range 2–296) months). Four patients (2·2 per cent) developed recurrence in group 1 and 16 (12·5 per cent) in group 2. The mean time to recurrence was 84·5 (range 49–143) months in group 1 and 45·3 (range 2–74) months in group 2. All patients in group 1 and 14 of 16 in group 2 died from recurrent disease.
Conclusion: Follow-up of patients with a melanoma less than 0·76 mm thick is not worthwhile. All recurrences would have been detected by annual review for 7 years in patients with melanomas between 0·76 and 1·5 mm thick.

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Introduction

The value of follow-up in patients who have undergone treatment for cancer remains debatable. There is considerable doubt whether the prognosis of these patients is greatly affected. The situation is highlighted in cancers thought to have an excellent long-term prognosis. Among this group are patients who have been treated for a thin melanoma. The aim of this study was to assess the value of follow-up in patients with melanomas less than 1·5 mm thick as measured on the Breslow scale[1].

Patients and methods

The study group comprised all patients with a melanoma less than 1·5 mm thick who presented to the Cardiff Melanoma Clinic, from its inception in 1971 up to, and including, the end of 1994. Follow-up was complete to this date.

All information regarding the patients is kept in ledgers. This information includes basic demographic data, tumour data with regard to site and history, treatments performed, final histological information including Breslow thickness and Clark's level, and follow-up data.

The patients were divided into two groups to allow meaningful comparison. Patients in group 1 had melanomas less than 0·76 mm thick and those in group 2 had melanomas 0·76–1·5 mm thick. A standard protocol was used for follow-up in each group. Group 1 patients were followed up annually, those in group 2 (and all other patients attending the clinic) were followed up every 2 months for the first 2 years after treatment, every 3 months for the next 2 years, every 4 months for the fifth year and annually thereafter. At each review the patient's entire skin surface was examined, together with all regional lymph node areas. No routine investigations were performed. The time to recurrence was defined as the time from definitive surgical management to confirmation of recurrent disease. The study groups were followed up in the melanoma clinic only. Patients with dysplastic naevus syndrome and other high-risk groups were not included.

All statistical analyses were performed using the χ^2 test for contingency tables, using the Minitab software package (Minitab, State College, Pennsylvania, USA).

Results

During the study 306 patients with a melanoma less than 1·5 mm thick were referred to the Cardiff Melanoma Clinic. Of these, 178 patients had a melanoma less than 0·76 mm thick (group 1) and 128 patients had a melanoma between 0·76 and 1·5 mm thick (group 2). The two groups were well matched for age, sex and length of follow-up (*Table 1*). In group 1 47·8 per cent of patients had a melanoma on the extremities, 31·5 per cent on the trunk and 20·8 per cent on the head and neck; respective figures in group 2 were 63·3, 27·3 and 9·4 per cent. There was a significant association between Clark's level and the thickness of the melanoma (*Table 1*).

The mean follow-up for patients in group 1 was 88·6 (range 4–296) months and that for group 2 was 80·4 (range 2–296) months. Three patients in group 1 and one in group 2 have been lost to follow-up. One patient from each group has emigrated after 90 and 122 months, respectively, but data from these two patients are included in the study. Five patients in group 1 and three in group 2 died for reasons unrelated to the melanoma; they are also included in the follow-up data. In total, four patients (2·2 per cent) in group 1 and 16 (12·5 per cent) in group 2 developed recurrent disease. All patients with recurrent disease in group 1 died as a result of the recurrent disease, as did 14 of 16 in group 2. The mean time from detection of recurrence to death was 1 month in group 1 and 13 months in group 2. Of significance is the fact that all patients with recurrent disease in group 1 presented with untreatable, widespread metastatic disease. All such recurrences were detected by a clinician in the follow-up clinic. In group 2, one patient developed local recurrence, one patient in-transit recurrence, three patients subcutaneous recurrence, seven nodal metastases and four distant metastases. In 13 of the 16 patients a clinician detected the recurrent disease in the follow-up clinic.

Table 1 Demographic details of patients with melanoma

	Melanoma thickness (mm)	
	< 0·76	0·76–1·5
Age (years)*	50·6 (8–87)	50·6 (19–89)
Sex (M : F)*	43 : 135	43 : 85
Site		
Head/neck	37	12
Trunk	56	35
Scalp	0	0
Extremities	85	81
Clark's level		
I–II	125	14
III–IV	30	87†
Follow-up (months)*	88·6 (4–296)	80·4 (2–296)
Time to recurrence (months)*	84·5	45·3

*Values are mean (range). †$P < 0.0001$ (χ^2 test)

Discussion

The only absolute benefit of follow-up for melanoma would be an improvement in prognosis. If there is no benefit in prognosis then follow-up could be deemed unnecessary. This is highlighted by thin melanomas less than 1·5 mm thick on the Breslow scale[1] which, because of increasing public awareness, have become an important health-care issue[2].

Some authors have argued that all patients who have had a melanoma should be followed up indefinitely[3] because the risk of recurrent disease is maintained irrespective of melanoma thickness, and many patients will develop recurrent disease more than 10 years after initial treatment[4,5]. Others have argued that patient self-examination is optimal, with open access to a clinic should any abnormality be detected. Follow-up clinics run by nurse practitioners can free up medical manpower as well as offering continuity of care[6]. However, Shumate and colleagues[7] demonstrated that in two groups of patients undergoing follow-up, one who attended as arranged and a second who attended earlier than planned, there was no difference in survival, thereby questioning the absolute value of clinical follow-up.

The patients in the present study were similar to those of other studies with regard to age, sex and proportion of patients with recurrent disease[8,9].

Many studies have evaluated prognostic factors for melanoma. Breslow[1] was the first to demonstrate that prognosis was related to the thickness of the melanoma. Clark *et al.*[10] later showed that the level of invasion of melanoma cells through the skin was also related to prognosis. Other studies have confirmed these original observations[11] as well as recording multivariate analyses relating to overall prognosis[12].

Thin melanomas of less than 0·76 mm are generally accepted to have an excellent prognosis, although there are a few reports in which the prognosis was not as good as expected. Thin melanomas with invasion to Clark's level IV carry a guarded prognosis although the numbers in this study were very small[13]. Level of invasion and site of primary tumour[14,15] are factors predictive of a poor outcome for patients with melanomas between 0·76 and 1·5 mm thick.

The recurrence rate of melanomas less than 0·76 mm thick in the present study was similar to the 2·7 per cent reported by Mansson-Brahme *et al.*[8] but less than the 4·8 per cent by Slingluff[16] and the 8·6 per cent by Pontikes and colleagues[17]. Other groups have reported that the extent of vascularization[18] and depth of invasion[13,17,19] can be used to select patients with a poor prognosis. Patients with melanomas less than 0·76 mm thick do occasionally develop metastases, but in the present study all presented with terminal disease. Slingluff and Seigler[16] have established risk factors for recurrence for patients with melanomas less than 0·76 mm thick. These are two clinical (male sex and axial primary lesion) and two histological (Clark's level IV and severe regression) factors. Three risk groups can be described depending on the number of factors present. The recurrence rate of melanomas 0·76–1·5 mm thick in this study was also consistent with values of 11 and 17 per cent for melanomas of equivalent thickness, as reported by Buttner and co-workers[20] and Schuchter *et al.*[12] respectively.

The risk of death from melanoma is linearly related to tumour thickness from 0 1 to 6·0 mm, with a 10-year survival rate of 96·3 and 80·9 per cent in groups similar to those in the present study, with broadly similar outcomes[20]. Guerry *et al.*[21] showed that the presence of a radial growth phase only in cutaneous melanomas resulted in a perfect metastasis-free survival in 161 patients followed up for a median of 13·7 years. However, in a follow-up study, only 3·4 per cent of 0·76–1·69-mm lesions had a radial growth phase only compared with 48·3 per cent of lesions less than 0·76 mm thick[22].

On the basis of these results, patients with a melanoma less than 0·76 mm thick require no follow-up. The situation for patients with a 0·76–1·5-mm melanoma is less clear. The majority of patients in this study presented with recurrent disease between 4 and 8 years after surgery. The initial follow-up was not helpful. The fact that the patients survived a mean 13 months after detection and treatment of recurrence could justify annual follow-up (particularly if factors predictive of a higher risk of recurrence could be determined).

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Original article

Treatment of gallbladder cancer by radical resection

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Background: The use of radical resection for gallbladder cancer is controversial. This study evaluated results of resection for gallbladder cancer and analysed prognostic factors.
Methods: A retrospective review of 135 patients who underwent surgical resection for gallbladder cancer between 1976 and 1998 was performed. Of these, 123 patients underwent radical resection and the remaining 12 had palliative resection. The resections included 32 hepatopancreatoduodenectomies and 57 with adjuvant radiotherapy. Twelve prognostic factors were analysed. A subset of 96 patients with stage IV disease was analysed separately with respect to residual tumour level and adjuvant radiotherapy.
Results: Surgical resection was associated with a 5-year survival rate of 36 per cent, with a mean follow-up time of 870 days. Twenty-two patients have survived more than 5 years including three with stage IV disease. Overall operative morbidity and mortality rates were 13 and 4 per cent respectively. The 5-year survival rate decreased with disease stage: 100, 78, 69 and 11 per cent for stages I (n = 13), II (n = 19), III (n = 7) and IV (n = 96) respectively. Performance status, jaundice, histopathological type and grade, primary tumour, lymph node, distant metastasis, stage grouping, residual tumour level and adjuvant radiotherapy were significant prognostic factors.
Conclusion: With careful patient selection, radical resection for gallbladder cancer improves the prognosis with acceptable operative mortality and morbidity rates, even for stage IV disease, provided that complete gross tumour resection is combined with radiotherapy.

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Introduction

Although the majority of patients with gallbladder carcinoma present at late stages of the disease resulting in a dismal prognosis overall[1–5], recent reports suggest the efficacy of radical surgical approaches in enhancing the long-term survival of these patients[6–10]. However, the benefits of radical approaches, including hepatopancreaticoduodenectomy, to patients with advanced disease have not yet been proven statistically to exceed the risks of operative complications or death.

In this retrospective study, the effects of radical resection, including 32 hepatopancreaticoduodenectomies, on long-term survival and operative outcome were evaluated; furthermore, prognostic factors for survival were analysed.

Patients and methods

Between October 1976 and February 1998, 135 patients with gallbladder carcinoma underwent surgical resection in this hospital. Patients were followed up for a mean period of 870 (range 3–7051) days. Preoperative performance status of the patients was estimated by criteria of the Japan Society for Cancer Therapy[11]. Women outnumbered men by a ratio of 2·6 : 1; mean age of the patients was 65 (range 36–89) years. The cancers were classified using the tumour node metastasis (TNM) classification criteria[12]. Seventy-four patients had hyperbilirubinaemia on admission with preoperative maximum total serum bilirubin levels ranging from 19 to 751 (mean 186) µmol/l. Percutaneous transhepatic drainage was performed to relieve jaundice in 57 patients with a mean preoperative maximum serum bilirubin level of 229 µmol/l. After alleviation of jaundice, resection was performed following routine image diagnostic procedures.

Resection procedures and indications

A variety of resection procedures were applied, ranging from cholecystectomy to combined bile duct resection, extended hepatectomy and hepatopancreaticoduodenectomy. Combined bile duct resection, defined as a bile duct

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resection of the main hepatic ducts to above the primary bifurcation and down to the intrapancreatic portion, was used in patients with obstructive or narrowing changes of the bile duct. Pancreaticoduodenectomy was used for patients with extensive peripancreatic lymph node metastases and/or involvement of the head of the pancreas. Hepatic bisegmentectomy (S4–5)[9] was carried out when direct tumour extension to these segments was within the resection margin or when the tumour extended bilaterally to the main hepatic bile ducts. Resection of the caudate lobe was essential when tumour extension to the left hepatic duct reached the bifurcation of the branch to the caudate lobe. Wedge resection of the gallbladder fossa was used when the tumour was located on the fossa without evident invasion into the hepatic parenchyma.

Nodes in the hepatoduodenal ligament and nodes of the right side of the coeliac trunk, around the common hepatic artery, were dissected as a standard procedure regardless of the stage of disease. Additionally, nodes of the periportal portion beneath the pancreas and the right side of the superior mesenteric artery, and the nodes of the right side of the aorta down below the bifurcation of the left renal vein, were dissected routinely in patients with swollen N_2 nodes.

Major vessels were reconstructed following resection of the portal vein and/or hepatic artery in 25 patients. The antrum of the stomach and the first portion of the duodenum were the organs most frequently resected, followed by the transverse colon. Of patients with stage IV disease, 78 per cent (75 of 96) had combination resections of these alimentary tract organs.

Adjuvant radiotherapy

Adjuvant radiotherapy was applied as reported previously[9,13]. Briefly, when preoperative images suggested the presence of local residual disease, intraoperative radiation therapy was planned. However, it was not always performed because of availability. Intraoperative radiation therapy was targeted to the stumps of the hepatic ducts, surrounding hepatic parenchyma, the hepatic artery and portal vein. A mean single dose of 21·3 (range 15–30) Gy was delivered just after resection. Postoperative radiotherapy was administered when pathological evaluation demonstrated positive surgical margins. However, it was not given to patients in poor medical condition or with distant metastasis, or if the patient refused. The radiation field included the hepaticojejunostomy, and the portal, coeliac and superior mesenteric arteries. A mean total dose of 38·9 Gy was given using a fraction size of 1·8–2·0 Gy 6–8 weeks after resection.

Statistical analysis

Survival was estimated by the Kaplan–Meier method and the differences among groups were tested by the log rank test. The Cox univariate and multivariate analysis was performed to determine prognostic factors for survival. All results were checked for the assumption of equality of slopes of log-transformed data that this method requires; only metastasis was excluded from further analysis owing to violation of this assumption. For the multivariate analysis of survival, TNM stage grouping and its defining factors were not used simultaneously because of the high correlation coefficient[14]. Histopathological grade was excluded from multivariate analysis because this classification is used only for adenocarcinoma. Radiotherapy was also excluded from multivariate analysis because 89 per cent (51 of 57) of all patients who received radiotherapy had stage IV disease.

Results

Stage and resection procedures

TNM stage in the 135 patients who underwent resection is summarized in *Table 1*. No T_1 tumour had metastasized. However, four of 24 T_2, three of nine T_3 and 44 of 89 T_4 tumours had distant metastases. It was confirmed at or after operation that 51 (53 per cent) of 96 patients with stage IV disease had distant metastases on lymph nodes beyond the N_2 region and/or on the liver, the peritoneum or the lung.

Table 1 Stage grouping of the resected patients

T	$N_0 M_0$ (n = 47)	$N_1 M_0$ (n = 8)	$N_2 M_0$ (n = 28)	$N_0 M_1$ (n = 3)	$N_1 M_1$ (n = 3)	$N_2 M_1$ (n = 45)
T_1 (n = 13)	13*	0‡	0	0	0	0
T_2 (n = 24)	19†	1‡	0	0	0	4
T_3 (n = 9)	4‡	1‡	1‡	0	1	2
T_4 (n = 89)	11	6	28	3	2	39

Lymph node metastasis beyond N_2 classified as M_1. Disease was classified as stage IV except *stage I, †stage II and ‡stage III

Every resection was carried out with curative intent except simple cholecystectomy applied to 12 patients with stage IV disease. For patients with advanced disease, three major optional procedures were performed according to the mode of tumour extension. The most frequent option was combined bile duct resection (98 patients), followed by liver resection, consisting of wedge resection, bisegmentectomy and extended lobectomy, and pancreaticoduodenectomy (35 patients, including 32 hepatopancreaticoduodenectomies). Radical resection achieved complete tumour removal at the microscopic level in all but one patient with disease less advanced than stage III. However, only 11 of 96 patients with stage IV disease benefited from radical approaches and 62 of them still had microscopic residues.

Operative complications and deaths

Among patients with stage I–III disease, no major postoperative complications occurred regardless of the resection procedure. However, of 96 patients with stage IV disease, 17 developed major complications, including one case of anastomotic leakage, five of liver abscess, two of pyothorax, 11 of sepsis, four of intra-abdominal and/or gastrointestinal bleeding, three of liver failure, eight of multiple organ failure and two others; some patients had multiple complications. Between 39 and 368 days after operation, seven patients died from lethal complications related to the surgical resection or to such complications in combination with radiotherapy with or without cancerous lesions. Complications occurred more frequently after hepatopancreaticoduodenectomy than after major or bisegmental hepatectomy without pancreaticoduodenectomy (nine of 32 *versus* four of 39 per cent). The 30-day operative death rate was 4 per cent (five patients), giving a total treatment-related mortality rate of 9 per cent (12 of 135). There was no relationship between operative death and resection procedure.

Survival and prognostic factors

As of 31 May 1998, 44 (32·6 per cent) of the patients were alive after tumour resection; the overall 5-year cumulative survival rate and median survival time were 36 per cent and 507 days respectively. Of these, 22 have survived for more than 5 years and three had stage IV disease. The resections of two of the three patients with stage IV disease were incomplete at the microscopic level but were followed by radiotherapy.

Univariate analysis revealed that survival was significantly related to ten factors: preoperative performance status and jaundice, histopathological type and grade, T, N and M factors of the TNM system (*Table 2*), TNM stage grouping (*Fig. 1*), residual tumour and adjuvant radiotherapy. Survival was not significantly related to age (less than 65 *versus* 65 or more years) ($P = 0·4891$) or sex ($P = 0·0750$).

The 5-year survival rates were 78, 64 and 28 per cent for performance status 0, 1 and 2 respectively. No patient with performance status 3 survived 5 years. The 5-year survival rate of patients without jaundice ($n = 61$) was 55 per cent, while that of the jaundiced patients ($n = 74$) was 12 per cent with a median survival time of 396 days.

When the radical resection was complete at the microscopic level ($n = 49$), the 5-year survival rate was 73 per cent, but when it was incomplete this rate was only 15 per cent, despite macroscopically complete resection ($n = 63$). However, the distribution of disease stages in these two groups was significantly different: the group with no residual tumour included 31 patients with early stage I and II disease and 11 with stage IV disease, while all patients with microscopic residue had stage IV disease, except one with stage I disease. Among patients with macroscopic residual tumour ($n = 23$), the longest survival time was only 656 days.

The separate analysis of survival in relation to radiotherapy ($n = 96$) showed significantly better survival among patients who had radiotherapy compared with those who had resection alone ($P = 0·0197$). The 5-year survival rate and median survival time in the two groups were 14 per cent and 396 days, and 6 per cent and 194 days respectively. For patients with microscopic residual disease ($n = 35$), the 5-year survival rate and median survival time improved significantly ($P = 0·0082$) to 19 per cent and 463 days respectively. However, no significant improvement was detected after using adjuvant radiation for patients with no microscopic ($n = 5$) or

Table 2 Five-year survival rates by tumour node metastasis definitive factors ($n = 135$)

Definitive factors of TNM	No of patients	5-year survival rate(%)	P*
T stage			< 0·0001
T_1	13	100	
T_2	24	69·7(10·7)	
T_3	9	50·0(18·6)	
T_4	89	9·1(4·8)	
N stage			< 0·0001
N_0	50	70·4(7·5)	
N_1	11	48·5(16·4)	
N_2	74	5·9(3·6)	
M stage			< 0·0001
M_0	84	51·5(3·6)	
M_1	51	4·8(4·9)	

Values in parentheses are standard errors. TNM, tumour node metastasis. *Log rank test

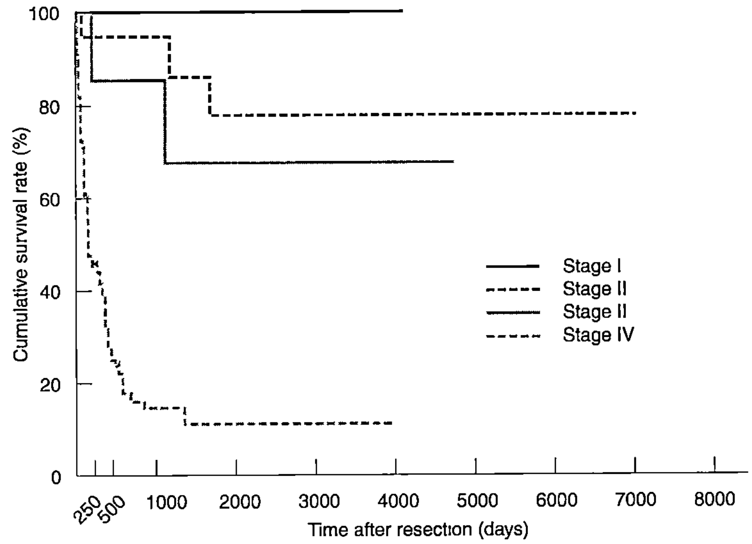

Fig. 1 Survival after resection of gallbladder cancer in accordance with pathologic TNM stage grouping. $P < 0{\cdot}0001$ (log rank test)

No at risk

Stage								
I ($n = 13$)	13	13	10	6	5	1	0	0
II ($n = 19$)	18	16	11	8	3	2	2	1
III ($n = 7$)	7	6	6	3	2	2	1	0
IV ($n = 96$)	39	18	7	3	2	1	0	0

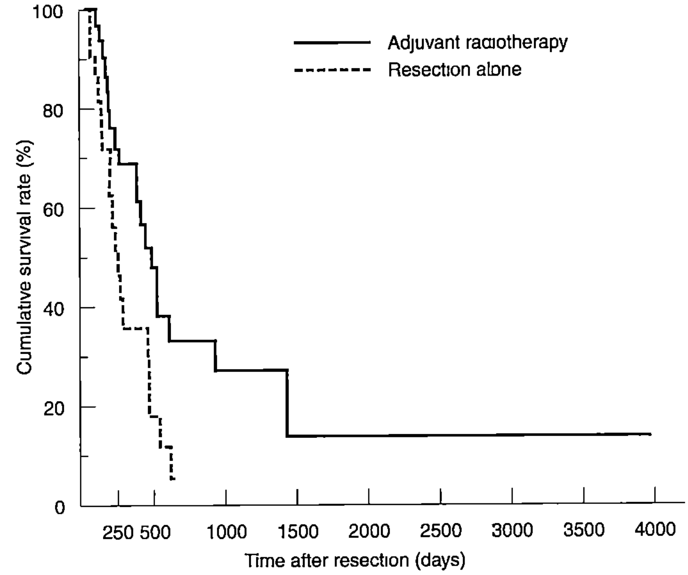

Fig. 2 Survival after radical resection of T4 tumour in patients who did or did not undergo adjuvant radiotherapy to microscopic residual tumour. $P = 0{\cdot}0167$ (log rank test)

No. at risk

Adjuvant ($n = 32$)	19	8	5	1	1	1
Resection alone ($n = 25$)	8	3	0	0	0	0

macroscopic ($n = 11$) tumour residue. *Fig. 2* shows survival of patients with T4 tumours.

Multivariate analysis among the eight prognostic factors revealed that sex, T, N and residual tumour had significantly higher risk ratios; histopathological type (adenocarcinoma *versus* non-adenocarcinoma) had an almost significant ($P = 0{\cdot}0521$) risk ratio of 1·909. The factors producing the greatest risk were residual tumour followed by T and N; the risk ratios of these factors were 3·8, 4·0 and 2·9 respectively. The risk ratio of the TNM grouping, estimated separately from the T, N and M variables, was highest at 11·7 (95 per cent confidence interval 4·3–31·7).

Discussion

The 5-year survival rate following surgery for gallbladder cancer has been reported to be between 5 and 13 per cent in the recent literature[1–5], excluding a recent study of a small number of resected cases[15]. Such poor surgical results are likely to be related to the high proportion of patients with advanced disease and possibly inadequate management to prevent locoregional tumour regrowth. Recent reports suggest that extensive aggressive resection using hepatopancreaticoduodenectomy is feasible with the possibility of a better outcome than is usual in patients with advanced gallbladder cancer[6–10]. The potential benefit of combining radiation and aggressive resection, including hepatopancreaticoduodenectomy, for stage IV gallbladder carcinoma was pointed out in a previous report[9].

The best survival rate according to major histopathological type was observed for adenocarcinoma, which was associated with a 5-year survival rate of 39 per cent, similar to the 32 per cent reported by Henson *et al.*[16].

When deciding on resection procedures, the T and N categories are important factors other than M that affect survival significantly (*Table 2*). T_1 disease, in which the lamina propria or muscle layer is invaded, can be resected curatively by simple cholecystectomy. Although N_1 lymphadenectomy (nodes in the hepatoduodenal ligament) is not necessary for patients with T_1 disease, this procedure is advocated in all cases owing to the difficulty in distinguishing between T_1 and T_2 during operation. A 5-year survival rate of 100 per cent was obtained after simple cholecystectomy where there were neither involved lymph nodes nor distant metastases (*Table 1*). Five of 24 patients with T_2 tumour had metastases not only in N_1 but also beyond N_2. For T_2 disease, in which perimuscular connective tissue is invaded with no extension beyond the serosa or into the liver, extended cholecystectomy with combined bile duct resection together with lymphadenectomy covering N_2 is essential. Bisegmentectomy was performed for six and wedge resection for four patients with a T_2 tumour. However, taking into account the 70 per cent 5-year survival rate (*Table 2*), hepatic resection of any type might be unnecessary for a T_2 tumour on the visceral side of the gallbladder.

The gallbladder is contiguous with the cystic duct, bile duct, Glisson's capsule and the hepatoduodenal ligament; these, together with the lymphatic and neural tissues, hepatic arteries and portal veins, are covered by the serosa and peritoneum. Once cancer cells perforate the serosa, all these adjacent tissues and structures become candidates for *en bloc* resection. Consequently, pancreaticoduodenectomy and/or hepatic resection of various kinds with combined bile duct resection in accordance with evidence of cancer invasion should be an essential element of complete resection for patients with T_3/T_4 tumour. For some patients, resection of the adjacent alimentary tract should also be performed for complete resection. Furthermore, node dissection not only of N_1 and N_2 but also of para-aortic nodes must be included to achieve complete resection for patients with T_3/T_4 tumours. Following these principles, radical resection, ranging from cholecystectomy with combined bile duct resection to combined hepatopancreaticoduodenectomy, was performed for 86 patients with T_3 ($n = 8$) and T_4 ($n = 78$) disease. Even for patients with T_4 disease, in whom a radical resection achieved complete gross resection with a microscopically positive margin, long-term survival was improved significantly compared with that after resection that failed to remove macroscopic lesions.

The main limitation to success in radical resection of T_4 tumours is a positive resection margin that subsequently becomes the apparent source of locoregional recurrence. Although the efficacy of radiotherapy in gallbladder cancer has been controversial, a retrospective study of a small number of patients[17] reported improved survival using tolerable doses on microscopic or subclinical locoregional lesions. In the present series, applying radiation to microscopic residual tumour after radical resection of T_4 disease ($n = 32$) yielded significantly better 5-year survival rates and median survival than did resection alone.

Given the impracticality of randomized clinical trials, these results and those of others clearly indicate that radical resection will improve the long-term outcome for patients with gallbladder cancer. Furthermore, combining radiation therapy with complete gross resection in advanced disease will improve survival with acceptable mortality and morbidity rates.

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Original article

Characterization of the Kupffer cell response to exogenous endotoxin in a rodent model of obstructive jaundice

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Background: Sepsis and endotoxaemia occur frequently in biliary obstruction. Impaired Kupffer cell endocytosis is implicated in these events. Tumour necrosis factor and interleukin 6, secreted by Kupffer cells, are important mediators of sepsis. Kupffer cell clearance of endotoxin and secretion of cytokines in experimental obstructive jaundice were investigated.

Methods: Wistar rats were randomized to bile duct ligation, sham operation or control. Groups ($n = 8$) were studied 1 and 3 weeks after operation. Kupffer cell function was assessed using *in situ* hepatic perfusion.

Results: Clearance of endotoxin was significantly depressed 1 week (median (interquartile range) 20·3 (10·5–27·1) per cent) and 3 weeks (22·1 (20·2–23·2) per cent) after bile duct ligation compared with that in respective sham animals (35·5 (29·9–41·6) and 40·9 (37·7–47·0) per cent) and controls (39·5 (37·3–46·8) per cent). Secretion of tumour necrosis factor was significantly greater 1 week (1113·7 (706·5–1436·8) pg/ml) and 3 weeks (1118·2 (775·7–1484·1) pg/ml) following bile duct ligation compared with that in respective sham animals (114·3 (0–178·5) and 107·6 (63·7–166·4) pg/ml) and controls (0 (0–20·7) pg/ml). Interleukin 6 was not secreted by sham or control animals but was present in the perfusate from jaundiced animals at 1 and 3 weeks (52·5 (9·9–89·5) and 66·2 (60·2–193·1) pg/ml).

Conclusion: These data demonstrate simultaneous impairment of Kupffer cell clearance of endotoxin and increased secretion of proinflammatory cytokines in experimental obstructive jaundice. These diverse responses may contribute to the development of sepsis-related complications in biliary obstruction.

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Introduction

Gram-negative sepsis and its sequelae occur frequently in patients with extrahepatic obstructive jaundice following invasive diagnostic or therapeutic procedures. Kupffer cells, resident liver macrophages, constitute 80–90 per cent of the fixed-tissue mononuclear cell population. Positioned at the interface between the portal and systemic circulations, Kupffer cells are responsible for sequestering pathogenic substances including bacteria and toxins from the portal circulation[1]. Normally, small quantities of endotoxin in the portal circulation are cleared by Kupffer cells[2]. Kupffer cell activation and subsequent secretion of inflammatory mediators is fundamental to an effective immune response. Persistently high or overwhelming activation may result in an uncontrolled initiation of the proinflammatory cascade leading to the systemic inflammatory response syndrome and potentially to multiple organ dysfunction syndrome[3].

In obstructive jaundice, a combination of alterations in intestinal microflora, the absence of intraluminal bile salts, diminished hepatic immunoglobulin (Ig) A production and impaired intestinal mucosal integrity contribute to increased endotoxin concentration in the portal circulation[4–6]. Inadequate clearance of endotoxin by Kupffer cells, with 'spillover' of endotoxin into the systemic circulation, has been implicated in the pathophysiology of systemic endotoxaemia in obstructive jaundice[7].

Kupffer cells are the principal source of the pro-inflammatory cytokines tumour necrosis factor (TNF) and interleukin (IL) 6 within the liver. Excessive production of cytokines, with activation of the inflammatory cascade, may follow injury or infection[8]. Enhanced secretion of cytokines by the mononuclear phagocytic system has been associated with hepatic failure and alcoholic liver disease[9,10]. Experimental and clinical studies in obstructive jaundice have suggested increased cytokine secretion by peritoneal macrophages and peripheral blood monocytes[11–13]. In view of the evidence of functional heterogeneity within subpopulations of the mononuclear phagocytic system, conclusions on Kupffer cell secretory function cannot be drawn from these studies[14–16].

The use of isolated liver perfusion with haemoglobin-free Krebs–Henseleit bicarbonate buffer is an established method for the investigation of hepatic physiology, pathology and pharmacology[17]. This well established technique allows selective assessment of specific liver functions in the physiologically intact organ, isolated from the systemic circulation and the effects of other organ systems.

The aim of this experiment was to characterize the functional response of the Kupffer cell to experimental obstructive jaundice. The functions assessed were endocytosis of endotoxin and subsequent secretion of the cytokines TNF and IL-6.

Materials and methods

Immunologically mature male Wistar rats ($n = 40$; 250–300 g) were randomly allocated to one of three groups: bile duct ligation and division (BDL; $n = 16$), sham operation ($n = 16$) or control ($n = 8$). Anaesthesia was induced by intramuscular injection of ketamine 6 mg/100 g and xylazine 0·7 mg/100 g. Laparotomy was performed through a 1·5-cm upper midline incision. In animals undergoing BDL, 1 cm of the bile duct was mobilized, doubly ligated with 4/0 silk just below the insertion of the lowest lobar duct and divided. The abdomen was closed with 3/0 chromic catgut, and the animals were allowed to recover. Sham operation entailed laparotomy and mobilization of the bile duct only. The control group underwent no procedure. Animals had free access to drinking water and standard chow *ad libitum*. Groups of eight animals were studied at 1 and 3 weeks.

In situ hepatic perfusion

Following the induction of anaesthesia, the abdomen was opened with a generous cruciate incision. A 16-G cannula was secured in the portal vein with two 4/0 silk ties. The hepatic artery was ligated. The chest was opened by excising the sternum and a 14-G cannula was inserted through the right atrium and secured in the suprahepatic inferior vena cava. This procedure was terminal. Blood sampling and surgical isolation of the liver took less than 2 min. Immediately following cannulation, the isolated liver was perfused with pyrogen-free oxygenated Krebs–Henseleit buffer. After 10 min of equilibration, perfusion was switched to buffer containing 1·6 µg/ml fluorescein isothiocyanate (FITC)-labelled lipopolysaccharide (*Escherichia coli* 026 : B6; Sigma Aldrich, Poole, UK) at 30 ml/min for a further 10 min. Perfusion was subsequently re-established with endotoxin-free perfusate for 50 min.

Paired aliquots of influent and effluent perfusate were collected at 2-min intervals during the 10-min period of perfusion with endotoxin. Aliquots of effluent perfusate were also collected 20, 40 and 60 min following exposure to endotoxin for biochemical and cytokine analysis. Blood and perfusate samples were immediately placed on ice before centrifugation at 2000 r.p.m. for 10 min at 4°C (Mistral 3000I centrifuge; MSE, Rotherham, UK) and freezing at – 70°C pending assay. Previously validated criteria were used to assess liver viability[18]. Samples of effluent perfusate were collected at 20-min intervals and assayed for aspartate transaminase, alanine transaminase and lactate dehydrogenase. Following perfusion, samples of the liver were taken and fixed in 10 per cent neutral buffered formalin; 5-µm sections were prepared, stained with haematoxylin and eosin, and examined histologically to confirm satisfactory perfusion.

Endocytosis of endotoxin

The fluorescence intensity of influent and effluent samples of perfusate collected during the period of perfusion with FITC-labelled endotoxin was measured on a standard spectrofluorometer (emission 495 nm, excitation 520 nm, slit width 10 nm; LS50B; Perkin Elmer, Beaconsfield, UK). Kupffer cell clearance of endotoxin was calculated as the percentage reduction in fluorescence in effluent perfusate (F_E) compared with a paired influent sample (F_I): $(F_I - F_E/F_I) \times 100$.

Five measurements of endotoxin clearance were made at 2-min intervals during the period of perfusion with endotoxin, from which a mean value was calculated. Kupffer cell endocytosis of FITC-labelled endotoxin was confirmed in normal liver. After perfusion with fluorescein-labelled endotoxin for 10 min, the liver was snap-frozen in liquid nitrogen and 10-µm sections were cut. These were then examined unstained under an incidence fluorescence microscope with a supplementary EY 455 excitation filter (Olympus BH2; Olympus Optical, Tokyo, Japan).

Endotoxin

Endotoxin concentration was determined using a quantitative *Limulus* lysate chromogenic assay (Quadratech, Epsom, UK). The detection limit of the assay was 10 pg/ml, interassay coefficient of variation was less than 10 per cent and intra-assay coefficient of variation was less than 15 per cent.

Anticore glycolipid antibody

Cross-reactive IgG and IgM antibodies to the highly conserved inner core region of endotoxin of four Gram-negative enteric species (*E. coli*, *Pseudomonas aeruginosa*, *Salmonella typhimurium* and *Klebsiella aerogens*) were measured using an enzyme-linked immunosorbent assay technique based on the method described by Scott and Barclay[19] for human serum. The results were expressed as a percentage of values in control animals.

Proinflammatory cytokine measurement

Immunoreactive TNF in plasma and perfusate was measured using an enzyme-linked immunosorbent assay technique developed in this laboratory[20]. Briefly, a 96-well microtitre plate was coated with monoclonal antibody to murine TNF (TN3 19.12; Celltech, Slough, UK) which exhibits a high degree of cross-reactivity to rat TNF. TNF bound to the solid phase was detected using rabbit polyclonal antimurine TNF antibody (Bradsure Biologicals, Loughborough, UK) and donkey antirabbit horseradish peroxidase conjugate (Jackson Immunoresearch, West Grove, Pennsylvania, USA). Absorbance was read at 490 nm. The detection limit of the assay was 39·0 pg/ml, interassay coefficient of variation was 10 per cent and intra-assay coefficient of variation was 11 per cent.

Biologically active IL-6 was measured using a standard cytotoxicity assay based on the IL-6-dependent B9 hybridoma cell line (L. Aarden, University of Amsterdam, The Netherlands)[21]. The detection limit of the assay was 40·0 pg/ml, interassay coefficient of variation was less than 10 per cent and intra-assay coefficient of variation was less than 15 per cent.

Statistical analysis

Results are expressed as median (interquartile range) and were analysed with the Mann–Whitney *U* test. Significance was taken at $P < 0·05$. Analysis was performed with the software package Arcus Pro-Stat (I. E. Buckan, Oxford, UK).

Results

There were no deaths in any group during the study. Weight gain in jaundiced animals diminished during the first week. Subsequent changes paralleled those in sham and control animals in weeks 2 and 3. The plasma bilirubin level was significantly higher 1 week after BDL compared with that at 3 weeks (182 (160–242) *versus* 131 (123–157) µmol/l; $P = 0·013$).

Systemic endotoxaemia

One week after BDL, there was no significant increase in plasma endotoxin concentration compared with that in sham or control animals. Three weeks after BDL, endotoxin was significantly higher than at 1 week after ligation ($P = 0·001$), at 3 weeks after sham operation ($P = 0·014$) and that in controls ($P = 0·004$) (*Table 1*). Levels of IgG and IgM antibodies to core glycolipid were raised in both groups of jaundiced animals at 1 and 3 weeks, but to a greater extent at 3 weeks (IgG, $P = 0·04$; IgM, $P = 0·02$) (*Table 1*).

Plasma cytokine secretion

TNF was not detected in plasma from any animal. IL-6 was not detected in sham or control animals but was raised in both groups of jaundiced animals, significantly more so at 3 weeks (1 week after BDL, 260 (182–303) pg/ml; 3 weeks after BDL, 655 (414–769) pg/ml; $P = 0·004$).

In situ hepatic perfusion data

Kupffer cell clearance of endotoxin

There was no significant difference in clearance of endotoxin 1 and 3 weeks following sham operation and that in

Table 1 Systemic endotoxaemia

Group ($n = 8$)	Endotoxin (pg/ml)	EndoCAb IgG (% control)	EndoCAb IgM (% control)
	Indices of systemic endotoxaemia		
Control	4·0 (2·1–6·6)	—	—
1 week			
Sham	2·3 (0·4–4·1)	84·2 (77·1–147·4)	86·7 (84·1–152·0)
BDL	0·6 (0–4·6)	183·5 (127·0–218·7)†	132·1 (125·5–163·3)†
3 weeks			
Sham	2·0 (0·8–7·3)	146·5 (137·7–223·1)	135·2 (114·1–147·0)
BDL	9·6 (6·3–14·6)*	228·1 (198·2–249·3)†	175·1 (151·3–202·7)†

Values are median (interquartile range). EndoCAb, core glycolipid antibody, Ig, immunoglobulin, BDL, bile duct ligation and division. $^*P < 0·05$ *versus* 1 week after BDL, 1 and 3 weeks after sham operation and control, $^†P < 0·05$ *versus* respective sham and control (Mann–Whitney *U* test) controls. Clearance of endotoxin was significantly depressed 1 and 3 weeks after BDL compared with that in respective sham animals ($P = 0{\cdot}007$ and $P = 0{\cdot}002$ respectively). There was no significant difference in the extent of depression in animals 1 and 3 weeks after BDL (*Fig. 1*).

Kupffer cell tumour necrosis factor secretion

TNF was detected in the perfusate from sham and jaundiced animals 20 min after exposure to endotoxin. TNF concentration was significantly greater in the perfusate from jaundiced animals at 40 and 60 min compared with that from respective sham animals by a factor of approximately ten (secretion at 60 min: 1 week after BDL *versus* 1 week after sham, $P = 0{\cdot}0003$; 3 weeks after BDL *versus* 3 weeks after sham, $P = 0{\cdot}0002$) (*Fig. 2*).

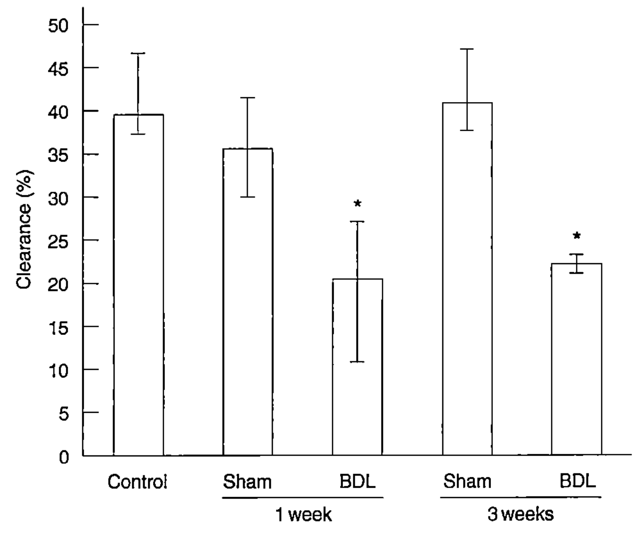

Fig. 1 Median (interquartile range) Kupffer cell clearance of fluorescein isothiocyanate-labelled lipopolysaccharide. BDL, bile duct ligation and division. $^{*}P < 0{\cdot}05$ *versus* respective sham and control (Mann–Whitney *U* test)

Kupffer cell interleukin 6 secretion

IL-6 was not detected in the perfusate from control or sham animals at 60 min. Following 60 min of perfusion IL-6 was detected in six of eight animals that had been jaundiced for 1 week (52·5 (9·9–89·5) pg/ml) and all eight animals jaundiced for 3 weeks (66·2 (60·2–193·1) pg/ml). There was no significant difference in the magnitude of the secretory response in jaundiced animals.

Discussion

Experimental and clinical studies in obstructive jaundice have demonstrated depression of a number of parameters of cellular immunity[22–28]. Investigations of mononuclear cell phagocytic function in obstructive jaundice have suggested that both systemic clearance and hepatic uptake of test probe are depressed in experimental obstructive jaundice although there have been conflicting results[29–34]. In the only study employing endotoxin as a probe, Adachi *et al.*[35] reported enhanced clearance of ^{51}Cr-labelled lipopolysaccharide in rats after BDL. In order to investigate Kupffer cell function specifically, Clements *et al.*[7] developed a novel application of *in situ* hepatic perfusion to measure Kupffer cell phagocytosis of latex microspheres by the isolated but physiologically intact liver. Clinical data on phagocytic function in obstructive jaundice are limited to studies showing impaired systemic clearance of microaggregated ^{125}I-labelled albumin[36,37].

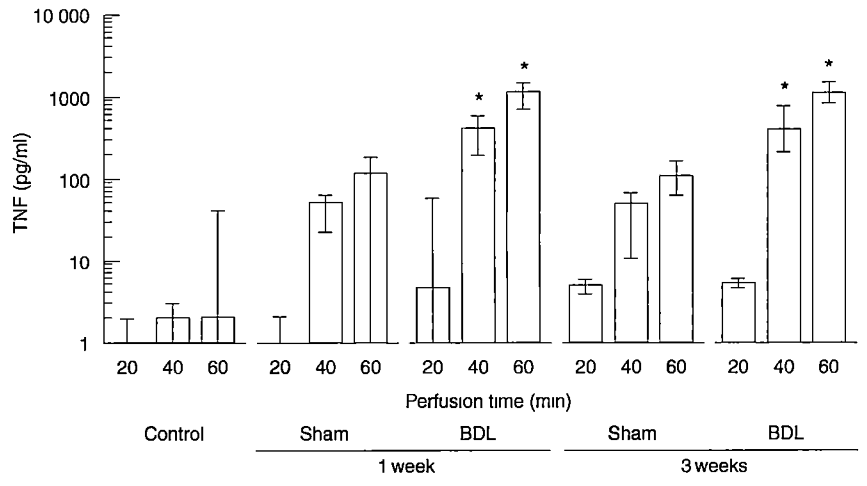

Fig. 2 Median (interquartile range) tumour necrosis factor (TNF) secretion 20, 40 and 60 min after exposure to fluorescein isothiocyanate-labelled lipopolysaccharide. BDL, bile duct ligation and division. $^{*}P < 0{\cdot}05$ *versus* respective sham and control (Mann–Whitney *U* test)

The present study has confirmed the occurrence of endotoxaemia in experimental biliary obstruction. The finding of systemic endotoxaemia is in agreement with previous studies and confirms consistent behaviour of the BDL model in these experiments[38].

Kupffer cell clearance of endotoxin, measured by *in situ* hepatic perfusion, was depressed by a factor of approximately 50 per cent following BDL at both 1 and 3 weeks suggesting that impairment in hepatic endocytic function is an early phenomenon which does not progress during the experimental period. Adachi *et al.*[35] reported increased systemic clearance of ^{51}Cr-labelled endotoxin, a measure of systemic endocytic function which may be enhanced in obstructive jaundice owing to increased uptake of endotoxin in other organs.

The finding that sham and control animals cleared only approximately 40 per cent of the endotoxin reflects the supraphysiological dose of endotoxin used in this experiment, which was necessary to ensure an adequate fluorescent signal. For the purposes of this study this was believed to be acceptable as the primary aim was to compare functional responses in this experimental model.

A number of factors may have contributed to the impairment in endocytic function demonstrated in this study. Although the number of Kupffer cells has been shown approximately to double in the liver following BDL, reduced expression of the major histocompatibility complex class II antigen has also been noted, suggesting diminished ability to process antigen[39]. A related explanation for the diminished endocytic function may be oversaturation of the system with endotoxin during the period of biliary occlusion. This has been suggested on the basis of morphological features observed on electron microscopy[39]. Alterations in sinusoidal blood flow, portasystemic shunting and lymphatic bypass may also contribute to systemic endotoxaemia in obstructive jaundice; however, these mechanisms alone cannot explain the functional derangement observed in experimental studies[40,41].

Immunoreactive TNF was not detected in the plasma from jaundiced animals. However, the perfusion data demonstrated that TNF secretion by the isolated but physiologically intact liver was approximately tenfold greater following BDL compared with that in the respective sham and control animals. There was no significant difference in either the kinetics or the magnitude of the secretory response in jaundiced animals at 1 and 3 weeks. Although other cell populations within the liver may be capable of secreting TNF, experimental studies of sepsis have shown the Kupffer cell to be the primary hepatic source of TNF in response to endotoxin[42].

Plasma IL-6 concentration was raised after BDL, and analysis of the perfusate from jaundiced animals demonstrated significant secretion of IL-6 after 60 min. IL-6 is secreted by a wide spectrum of cell types including immune effector cells (B and T lymphocytes, monocytes, alveolar macrophages and Kupffer cells), fibroblasts, enterocytes, fibroblasts and endothelial cells. Within the liver *in vivo* and *in vitro* studies have shown the Kupffer cell to be the principal source of IL-6 following stimulation with endotoxin, burn injury and trauma–haemorrhage[43,44].

In conclusion, it has been shown that hepatic clearance of endotoxin and secretion of cytokines respond in a diverse fashion to biliary obstruction. These specific responses of the Kupffer cell to obstructive jaundice may be central in the aetiology of systemic endotoxaemia and may contribute to the pathophysiology of septic complications in obstructive jaundice. The underlying control mechanisms require further investigation.

Acknowledgements

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Original article

Immunoglobulin A antibodies against *Chlamydia pneumoniae* are associated with expansion of abdominal aortic aneurysm

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Background: The aim of this study was to examine the possible association between the progression of small abdominal aortic aneurysm (AAA) and chronic infection with *Chlamydia pneumoniae*.

Methods: Patients from a hospital-based mass screening programme for AAA with annual follow-up (mean 2·7 years) were included. After initial interview, 139 men aged 65–73 years with a small AAA underwent examination and blood sampling. Immunoglobulin (Ig) G and IgA titres against *C. pneumoniae* were measured by a microimmunofluorescence test.

Results: Some 83 (95 per cent confidence interval 74–93) per cent of the men had an IgA titre of 20 or more, or an IgG titre of 32 or more. Men with an IgA titre of 20 or more had a 48 per cent higher AAA expansion rate than those with a titre of less than 20 (3·1 *versus* 2·1 mm/year; $P < 0·05$). Multiple linear and logistic regression analyses showed that an IgA titre of 20 or more was a significant independent predictor of increased AAA expansion, adjusted for known risk factors of expansion. Initial AAA size and serum total cholesterol level were also predictors of expansion.

Conclusion: A high proportion of men with a small AAA had signs of chronic infection with *C. pneumoniae*. Aneurysm progression correlated with evidence of chronic *C. pneumoniae* infection.

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Introduction

Seroepidemiological studies have shown an association between *Chlamydia pneumoniae* and atherosclerosis and acute myocardial infarction[1–7]. Furthermore, several studies have detected *C. pneumoniae* DNA and *C. pneumoniae* antigen in atherosclerotic lesions from coronary and carotid arteries, and in abdominal aortic aneurysms (AAAs)[8–15]. However, culture of *C. pneumoniae* has succeeded only once. Two relatively small controlled clinical trials randomized patients with ischaemic heart disease to antibiotic treatment or placebo[16,17]. Both trials showed a significant reduction in progression of ischaemic heart disease in patients who were receiving macrolide antibiotics. It is not known whether this is a result of the eradication of *C. pneumoniae* organisms or the macrolide's non-specific anti-inflammatory effect[18].

Small AAAs are usually not recommended for surgery because of the low risk of rupture. Some small AAAs continue to expand to dimensions that carry a high risk of rupture. Consequently, patients with a small AAA are offered regular ultrasonographic scans to check for expansion. This provides a unique opportunity to study the progression of an atherosclerotic disease that could be correlated with signs of chronic *C. pneumoniae* infection.

Patients and methods

From 1994 to 1996, 5470 men aged 65–73 years were invited to attend for ultrasonographic screening for AAA at the regional hospital in Viborg County, Denmark. Some 4165 (76 per cent) attended and were examined by a doctor and a nurse trained in ultrasonography. An AAA was diagnosed when the anteroposterior aortic diameter was 3 cm or more. Patients with an AAA of 5 cm or more were referred to a vascular surgeon. Men with an AAA of 3–4·9 cm were offered annual follow-up ultrasonographic examinations to check for expansion.

Medical history, present medication and smoking habits were recorded for each patient. Height and weight were measured. The highest brachial blood pressure and the lowest systolic ankle blood pressure were recorded. The forced vital capacity (FVC) and the volume expired during the first second of the FVC were measured with a mobile

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Table 1 Seropositivity for *Chlamydia pneumoniae* compared with expansion of small abdominal aortic aneurysms

	No. of patients*		Annual expansion (mm)			
	Seropositive	Seronegative	Seropositive†	Seronegative†	Difference‡	*P*§
IgA ≥ 20	94 (68)	45 (32)	3·1(2·9)	2·1(2·6)	1·0 (0·6–2·7)	0·003
IgG ≥ 32	104 (75)	35 (25)	3·0(2·9)	2·0(2·6)	1·0 (0·5–2·8)	0·005
IgA ≥ 20 or IgG ≥ 32	115 (83)	24 (17)	3·0(2·8)	1·8(2·7)	1·2 (0·9–3·4)	0·001
IgA ≥ 40	60 (43)	79 (57)	3·1(2·8)	2·2(2·9)	0·9 (–0·2 to 1·9)	0·09
IgG ≥ 64	78 (56)	61 (44)	3·1(2·6)	2·1(3·2)	0·9 (–0·1 to 2·0)	0·08
IgA ≥ 40 or IgG ≥ 64	86 (62)	53 (38)	3·0(2·5)	2·1(3·3)	0·9 (–0·2 to 1·9)	0·10

*Values in parentheses are percentages, values are †mean(s.d.) or ‡mean (95 per cent confidence interval). Ig, immunoglobulin. §*t* test

Table 2 Predictors of expansion of small abdominal aortic aneurysms by linear regression analysis

	Change in annual expansion rate (mm)		
	Model 1	Model 2	Model 3
IgA ≥ 20	1·84 (0·65–3·03)*		
IgG ≥ 32		1·22 (–0·04 to 2·48)	
IgA ≥ 20 or IgG ≥ 32			2·13 (0·76–3·50)*
AAA size (mm)*	0·21 (0·11–0·31)	0·23 (0·13–0·33)	0·23 (0·13–0·33)
Serum total cholesterol (mmol/l)*	0·57 (0·07–1·07)	0·55 (0·03–1·07)	0·60 (0·10–1·11)
Smoker (Yes, 1; No, 0)	0·78 (–0·33 to 1·89)	0·98 (–0·16 to 2·12)	1·02 (–0·08 to 2·12)
Age (years)	0·16 (–0·04 to 0·37)	0·10 (–0·11 to 0·31)	0·11 (–0·09 to 0·31)
Y-intercept	–21·096	–16·915	–18·957

Values in parentheses are 95 per cent confidence intervals Ig, immunoglobulin, AAA, abdominal aortic aneurysm. *$P < 0.05$

vitalograph[19]. Each patient had blood sampled at the initial visit. Plasma and serum were stored at – 21°C until analysis. Plasma was analysed for elastase–α_1-antitrypsin complexes[20], and serum for triglycerides, total cholesterol[21], and immunoglobulin (Ig) G and IgA antibodies against *C. pneumoniae* by means of microimmunofluorescence (MIF) tests[22].

Some 170 men (4 per cent) had an AAA; 21 aneurysms were more than 5 cm in diameter and were therefore referred for surgery. Of the remaining 149 patients, 139 (93 per cent) have now been followed for between 1 and 3 years: 73 for 3 years, 22 for 2 years, and 44 for 1 year. Aneurysm expansion rate was calculated as the annual change in the anteroposterior diameter during the observation period.

In order to validate the measurement of AAA diameter, 24 patients were imaged twice; 95 per cent of the second aortic measurements were within 2 mm of the first.

SPSS 6.1 (SPSS, Chicago, Illinois, USA) was used to perform Student's *t* test, Fisher's exact test, the χ^2 test, linear regression analysis and logistic regression analysis.

Results

An IgA titre of 20 or more against *C. pneumoniae*, an IgG titre of 32 or more, or a raised IgA or IgG titre as just defined, were all associated with increased mean annual aneurysm expansion (*Table 1*).

Table 3 Crude and adjusted odds ratios using annual expansion below or above 3 mm as a dependent variable and adjusting for expansion risk factors used in *Table 2*

	Crude odds ratio	Adjusted odds ratio
IgA ≥ 20	3·1 (1·1–8·9)*	8·2 (4·5–14·8)*
IgG ≥ 32	2·6 (0·9–7·8)	2·2 (0·8–5·9)
IgA ≥ 20 or IgG ≥ 32	14·7 (1·9–310·2)*	151·4 (0·6–3581·3)

Values in parentheses are 95 per cent confidence intervals. Ig, immunoglobulin. *$P < 0.05$

Table 2 shows a linear regression analysis with mean annual expansion as the dependent variable and the various serological definitions of chronic infection as independent predictors, adjusted for variables that have been reported to influence expansion, and age[23–28]. An IgA titre of 20 or more remained an independent predictor of expansion, and an IgA titre of 40 or greater became an independent predictor of expansion after adjusting for the risk factors of expansion. Initial AAA size and serum total cholesterol level remained predictors of expansion. When ankle : brachial pressure index, diastolic blood pressure, pulmonary function, serum triglycerides, plasma elastase–α_1-antitrypsin and steroid treatment were included in the multiple regression, none had any influence on aneurysm expansion rate or the serological association with expansion.

Even though the same scanner and observer were used at the initial and control scans, an intraobserver variation of 2–3 mm might be expected[29–31]. Consequently, logistic regression analyses were conducted using annual expansion below or above 3 mm as a dependent variable, adjusting for the risk factors of expansion used in the multiple linear regression analyses (*Table 3*). An IgA titre of 20 or more, an IgG titre of 32 or more, or raised IgA or IgG as just defined, were associated with expansion above 3 mm per year. An IgA titre of 20 or more remained a significant risk factor for expansion above 3 mm per year, with an adjusted odds ratio of 8·2. An IgA titre of 40 or more became a significant risk factor for expansion above 3 mm per year, with an adjusted odds ratio of 4·6.

Discussion

The duration of immune protection after infection with *C. pneumoniae* is limited[32–35], and persistent infection may occur since the host may be incapable of eradicating the organism[32,33,35,36]. Both persistent and repeated infections may cause intense inflammatory reactions[32,37].

Infection with *C. pneumoniae* is endemic, but epidemics lasting 2–3 years occur, followed by 3–10 years with a lower incidence[32,38,39]. Infants are seldom infected. The infection arises in preschool children and young adolescents, and increases with age, reaching a seroprevalence of 75 per cent in the elderly, indicating that the majority of the population have two to three reinfections during their lifetime[37].

The MIF test is specific for the species, and allows detection of the various immunoglobulin types against *C. pneumoniae*. IgA antibody titres usually decline and disappear 3–12 months after infection. Consequently, a persistently raised level of IgA is indicative of chronic infection. IgG antibodies may persist for some years[1,34,38,40,41]. A fourfold increase in IgG titre, or an IgM titre of 32 or more, approximately 3 weeks after onset indicates acute infection. The increase in IgG titres may be delayed until 8 weeks. An IgG titre of 128 or more is believed to indicate past or pre-existing infection but the persistence of short-lived IgA may be a better marker of chronic infection than IgG[2]. IgM is not detectable in reinfections. Consequently, in this study only IgA and IgG titres were analysed.

The study demonstrated a high prevalence of seropositivity of *C. pneumoniae* in patients with a small AAA. Saikku *et al.*[1] found that 20 of 40 men with acute myocardial infarction, 20 of 30 with angina pectoris, but only seven of 41 matched controls had raised levels of IgG and IgA antibodies against *C. pneumoniae*. Thus, the seroprevalence seems equal or even higher in men with AAA. Studies of the aneurysm wall with *C. pneumoniae*-specific polymerase chain reactions have demonstrated the presence of the bacterial DNA in only 50–60 per cent. Studies using both direct DNA detection in the aneurysm wall or atherosclerotic plaques and indirect serological detection have reported poor concordance between the two methods. In fact, direct detection of *C. pneumoniae* antigens and DNA in lesions seems more frequent in people with low rather than with high titres[3,42–45]. This is contrary to a dose–response reaction, which could have been expected. This inconsistency may be explained by substances in human specimens that inhibit the polymerase chain reaction, patchy occurrence in the plaques, or by the fact that some infections are over while serological signs remain, or that the titres defining a chronic infection are too high. As mentioned, the presence of IgA indicates a recent or present infection. The present infection may be acute or chronic. Chronic infection has the potential to produce progressive arterial degradation but can persist only where there is an insufficient immunological response. While high titres may be found in patients with past infections that were sufficiently eradicated by the immunological system, infections with low titres are more likely to be chronic. Consequently, a dose–response effect cannot be expected, and direct detection of DNA could be negative compared with the traditionally used high standard titres.

These observations suggest that chronic infection with *C. pneumoniae* may play a part in the pathogenesis of AAA. Standard serological values may be insufficient in the diagnosis of chronic infection. It may be hypothesized that macrolide treatment could prevent the progression of AAA and other atherosclerotic diseases. Some bacteria, especially Gram-positive cocci, readily become resistant to macrolide antibiotics. This resistance also involves clindamycin which is a powerful drug for managing resistant *Staphylococcus*. Consequently, the ecological consequences of widespread use of macrolide antibiotics as prophylaxis in the population may be serious. Randomized intervention trials are needed, not only to determine the effect of treatment but also to identify the potential benefits of macrolide treatment.

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Contribution of diet, tumour volume and patient-related factors to weight loss in patients with colorectal liver metastases

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Background: One of the difficulties in assessing the contribution of tumour-related factors to cancer cachexia is measurement of the extent of disease where dissemination to multiple organ sites has occurred.

Methods: In this study the extent of tumour (both tumour volume and increase in marker levels), diet and patient-related factors (appetite, metabolic hormones, immune activation, liver function and quality of life) were compared in patients with colorectal liver metastases who had lost at least 1 kg in body-weight (weight loss) and patients who had not lost 1 kg in body weight (stable weight) during the preceding month.

Results: Forty patients (22 men; 14 with weight loss) were studied. Liver metastasis volume was significantly greater in patients who lost weight than in those whose weight was stable (median (interquartile range) 1179 (245–1517) *versus* 119 (23–523) ml; $P = 0.003$). The prevalence of patients with raised levels of serum immune products was significantly greater in the weight loss group for soluble interleukin (IL) 2 receptor α (sIL2rα) ($P = 0.03$) and IL-6 ($P = 0.05$), but not for soluble tumour necrosis factor receptor 1 (sTNFr1) or neopterin. There were significant correlations between serum C-reactive protein and sIL2rα ($r_s = 0.68$, $P < 0.0001$) and IL-6 ($r_s = 0.46$, $P = 0.008$) but not sTNFr1 or neopterin levels. Significant differences in appetite, nausea, diet, energy intake, liver function tests and serum levels of metabolic hormones were not detected.

Conclusion: Weight loss in patients with colorectal liver metastases was not explained by changes in diet, quality of life, or hormones, but activation of the innate and incomplete activation of the acquired immune systems may be involved. Agents that attenuate either the acute-phase inflammatory response or T lymphocyte IL-2 receptor upregulation might reduce weight loss in patients with metastatic disease.

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Introduction

Suggested mechanisms for cancer-related weight loss include hormone-induced changes in metabolism[1], tumour-related immune activation with cytokine[2,3] release, alteration in diet or appetite[4] and reduced gastrointestinal nutrient absorption[5]. Weight loss is usually associated with advanced cancer[6] and one of the difficulties in assessing the contribution of tumour-related factors to weight loss is measurement of the extent of disease where dissemination to multiple organ sites has occurred.

Colorectal liver metastases are suited to the study of weight loss in advanced cancer because metastasis is predominantly to the liver[7] and tumour volume can be measured by hepatic computed tomography (CT)[8]. In this study the relative contributions of the extent of tumour (estimated by both tumour volume and increased levels of markers), diet and patient-related factors (appetite, metabolic hormones, immune activation, liver function and quality of life) to weight loss were assessed in patients with colorectal liver metastases.

Patients and methods

All patients in the study were seen at a colorectal oncology outpatient clinic in one hospital between January 1995 and January 1997. The inclusion criteria were that patients should have undergone excision of primary colorectal carcinoma more than 12 weeks previously, and have liver metastases but no other recurrent disease on abdominal and pelvic CT, as well as a normal chest radiograph.

Patients receiving chemotherapy or corticosteroids at the time of the study were excluded.

In accordance with previous evidence[9] that patients who have lost more than 1 kg in body-weight during the previous month have a reduced survival, such patients were allocated to a 'weight loss' group and those who had not lost 1 kg during the previous month to a 'stable weight' group. Body mass index (BMI) was derived from the quotient of body-weight in kg by the square of patient height in metres. Blood was assayed for serum carcinoembryonic antigen (CEA), albumin, alkaline phosphatase, cortisol, growth hormone, insulin, thyroid-stimulating hormone (TSH), C-reactive protein (CRP), soluble tumour necrosis factor receptor 1 (sTNFr1), interleukin (IL) 6, soluble IL-2 receptor α (sIL2rα) and neopterin, and plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin. All patients underwent blood sampling within 2 h of 11.00 hours following an overnight fast.

Measurement of serum cortisol and insulin levels was by automated enzyme-linked immunosorbent assay (ELISA) (ES 700; Boehringer Mannheim, Lewes, UK). Serum growth hormone levels were measured using the IDS immunoradiometric assay (OMNIA kit; IDS, Boldon, Tyne and Wear, UK), serum TSH by automated ELISA (ES 700; Boehringer Mannheim) and serum CEA by automated ELISA (Immulite; EURO DPC, Caernarfon, UK). Serum albumin, and plasma bilirubin, AST and ALT were measured using a Hitachi 7474 automated analyser (Boehringer Mannheim). CRP was measured by an automated immunoturbidimetric assay on an Olympus AU600 analyser (Olympus Diagnostic Systems, Eastleigh, UK), using reagents provided by the company and following their recommended procedures. Serum CRP concentrations of up to 10 mg/l were considered to be within the normal range. Serum IL-6, sTNFr1, sIL2rα and neopterin were measured by ELISA[10] using commercially available kits supplied by R and D Systems Europe, Abingdon, UK (IL6, sTNFr1, sIL2rα) and ICN Flow, Basingstoke, UK (neopterin). The sIL2rα assay coefficients of variation (supplied by the manufacturer) were less than 6·1 per cent (intra-assay) and less than 7·2 per cent (interassay); those for other immune product assays were within a similar range. Normal serum values (median (range)) reported by the suppliers were: IL-6, 1·6 (0·4–10·1) ng/l; sTNFr1, 1198 (749–1966) ng/l; sIL2rα, 1346 (676–2132) ng/l; and neopterin, less than 10 nmol/l. The upper value in each range was taken as the upper limit of normal.

Liver metastasis volume was measured from CT images taken within 14 days of blood sampling using a technique described previously[8]. Within the same time interval, all patients completed the Hospital Anxiety and Depression (HAD) scale[11], Rotterdam Symptom Checklist (RSC)[12] and Sickness Impact Profile (SIP)[13] quality of life instruments, and a previously validated short dietary questionnaire[14] enquiring about food intake over the previous week.

All variables were expressed as median (interquartile range). Differences between variables were assessed either by Mann–Whitney *U*, paired Wilcoxon or Fisher's tests, or log rank test of Kaplan–Meier distributions, as indicated. Spearman's test was used for correlations and logistic regression analysis as described previously[15]. The probability of error in the estimation of regression coefficients was determined using the one-sided Wald statistic[16].

The study was approved by the Chelsea and Westminster Hospital Ethics Committee.

Results

Forty patients (22 men; 14 with weight loss) were studied. The median survival of patients in the weight loss group (157 (76–231) days) was significantly shorter than that of patients in the stable weight group (403 (247 to more than 500) days) ($P = 0{\cdot}0004$, log rank test).

Body-weight and body mass index

There was no significant difference in either body-weight (weight loss, 70·8 (62·3–74·5) kg; stable weight, 73·4 (70·0–79·0) kg; $P = 0{\cdot}202$, Mann–Whitney *U* test) or BMI (25·1 (21·5–27·5) *versus* 26·1 (23·1–28·3); $P = 0{\cdot}15$, Mann–Whitney *U* test) at the time of study. A significant BMI reduction ($P = 0{\cdot}031$, paired Wilcoxon test) occurred in the weight loss group between the time of study and 1 month later, but no significant BMI reduction was detected within 3 months of the study in the stable weight group (*Fig. 1*). BMI was significantly reduced ($P = 0{\cdot}035$, Mann–Whitney *U* test) in the weight loss group compared with stable weight group at 1 month after study entry.

Quality of life

Significant increases between weight loss and stable weight groups were detected for HAD scale depression (8·0 (3·0–9·0) *versus* 3·5 (2·0–6·5); $P = 0{\cdot}01$, Mann–Whitney *U* test), RSC physical symptom (17 (13–21) *versus* 11 (8–18); $P = 0{\cdot}05$) and SIP (158 (50–200) *versus* 66 (13–124); $P = 0{\cdot}02$) scores. Significant differences in HAD scale anxiety and RSC psychosocial scores were not detected.

Appetite and diet

There were no significant differences (Fisher's test) in the distribution of answers to quality of life questions concerning lack of appetite (RSC question 1), nausea (RSC10), vomiting (RSC14) or eating (SIPe) between the

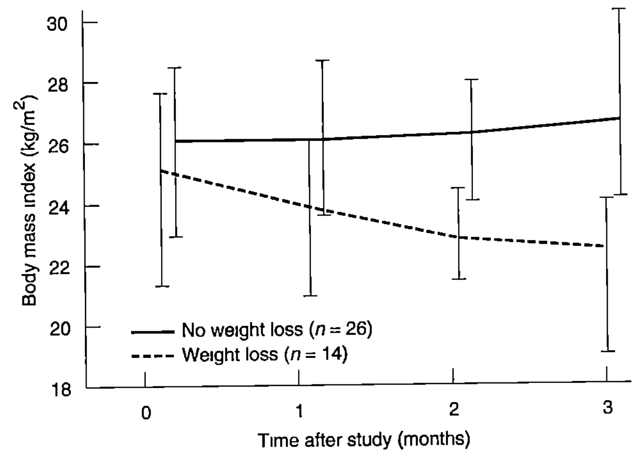

Fig. 1 Median (interquartile range) body mass index (BMI) by time from the day of study. The rate of BMI decrease was greatest in the weight loss group during the first month after the study. There was no significant BMI change in the stable weight group during the first 3 months from the day of study

two groups. Similarly, in the diet questionnaire, significant differences in dietary intake of protein, fat, sugar, starch, fibre, alcohol or in daily energy intake were not detected (Mann–Whitney U test) between weight loss and stable weight groups, whether corrected or uncorrected for body-weight. In addition, no significant difference in daily energy intake was identified in patients with a CRP of greater than 10 mg/l compared with those with a CRP of less than 10 mg/l (Mann–Whitney U test).

Tumour bulk

Liver metastasis volume was significantly greater in the weight loss group compared with the stable weight group (1179 (245–1517) *versus* 119 (23–523) ml; P = 0·003, Mann–Whitney U test). The serum CEA level was also significantly greater in the weight loss compared with stable weight group (606 (111–155) *versus* 65 (19–290) units; P = 0·01, Mann–Whitney U test).

Immune products

There was a significant increase in CRP level in the weight loss compared with the stable weight group (61 (23–87) *versus* 10 (1–24) mg/l; P = 0·02, Mann–Whitney U test). There was also a significant increase in serum sIL2rα level in the weight loss group (2174 (1039–3114) *versus* 1034 (667–1773) ng/l; P = 0·05, Mann–Whitney U test). Significant increases in serum IL-6, sTNFr1 and neopterin levels between the groups were not detected (Mann–Whitney U test). The prevalence of patients with a raised serum immune product level above normal was significantly greater in the weight loss compared with the stable weight group for sIL2rα (six of 11 *versus* four of 23; P = 0·03, Fisher's test) and IL-6 (seven of 11 *versus* seven of 23; P = 0·05), but not for sTNFr1 or neopterin. There were significant correlations between serum CRP and serum sIL2rα (r_S = 0·68, $P < 0·0001$) and IL-6 (r_S = 0·46, P = 0·008) but not sTNFr1 or neopterin levels.

Metabolic hormones

There were no significant differences in serum levels of insulin, growth hormone, TSH or cortisol between the two groups (Mann–Whitney U tests).

Liver function tests

The serum alkaline phosphatase level was raised significantly more in the weight loss than the stable weight group (738 (237–1154) *versus* 280 (159–427) units/l; P = 0·002, Mann–Whitney U test). Significant differences in plasma bilirubin, AST and ALT, or serum albumin were not detected (Mann–Whitney U tests).

Logistic regression analysis of variables that were significantly different between the two groups selected serum CEA and sIL2rα as the two independent variables on which weight loss most depended (*Table 1*).

Table 1 Logistic regression analysis of factors found to correlate significantly with weight loss in patients with colorectal liver metastases

Variable	Step 0	Regression coefficient	P*	Step 1	Regression coefficient	P*
Serum carcino-embryonic antigen	0·003	1·42(0·63)	0·01	Selected	1·72(1·04)	0·05
Serum sIL2rα	0·004			0·020	3·32(2·06)	0·05
Serum alkaline phosphatase	0·023			0·029		
Tumour volume	0·080			0·024		
Serum IL-6	0·340			0·486		
C-reactive protein	0·349			0·288		

Values in parentheses are standard errors. *Probability of error in estimation of regression coefficient. The strongest predictors of weight loss were serum carcinoembryonic antigen and the soluble α fragment of the interleukin (IL) 2 receptor (sIL2rα), in that order

Discussion

Although loss of more than 1 kg body-weight during the previous month[9] was associated with a tenfold increase in median liver metastasis volume, the difference in body-weight between the weight loss and stable weight groups at the time of study was small (median 2·6 kg). The weight difference between the groups might be reduced because patients in the stable weight group may also have lost some weight without fulfilling the criterion required for the weight loss group (loss of 1 kg in the preceding month). However, the finding that there was no weight loss in the stable weight group during the 3 months after the study makes it unlikely that these patients had lost weight during the preceding month. The extent of weight loss in the weight loss group did not reach the level of 11 per cent of premorbid weight, which has been reported for pancreatic cancer[17], until 3 months after the study by which time most patients had reached the terminal stage of disease. Thus weight loss from colorectal liver metastases was associated with a large tumour volume, and with an equivalent weight loss to that in pancreatic cancer being reached only by the terminal stage of the natural history.

Since the study was undertaken before the greatest fall in BMI (0–1 month after the study), it is likely that the abnormalities detected were a consequence of the disease rather than the weight loss. The food frequency questionnaire is a well established technique for identifying current food intake. The accuracy of dietary questionnaires may be limited by patient recall when questioned about diet during the previous month, but prospective data collection can influence eating behaviour and methods based on weighed dietary intake are too arduous for this group of patients.

Although the deterioration in depression and physical symptoms that is associated with larger liver metastases[18] was identified in patients who lost weight, this deterioration was not associated with a significant reduction in appetite or food and energy intake. Wigmore *et al.*[17] reported that energy intake was reduced by 29 per cent in patients with pancreatic cancer in whom an acute-phase protein response, defined by a serum CRP level of greater than 10 mg/l, was identified. In the present study of patients with colorectal liver metastases, significant decreases in food or energy intake did not correlate with a raised CRP level. This may be one explanation for the greater weight loss reported with pancreatic cancer compared with colorectal cancer.

Monocyte/macrophage release[19] of the cytokine IL-6 stimulates hepatocyte CRP production[20,21] with activation of an acute-phase protein response which influences protein turnover and energy expenditure[22]. In the present study, the correlation of raised serum IL-6 and CRP levels with weight loss was consistent with involvement of the acute-phase protein response[3] in the weight loss associated with colorectal liver metastases[23]. The absence of any association between serum sTNFr1 or neopterin levels and weight loss suggests that tumour necrosis factor[23] and interferon activation[24] of monocytes/macrophages did not have a role in weight loss, but this should be interpreted with caution as these effects may have been apparent only at the local cellular level.

Release of sIL2rα from the T lymphocyte surface into the serum is thought to occur after T lymphocyte upregulation[25], and raised serum sIL2rα levels have been reported previously in advanced colorectal cancer[26]. The finding that sIL2rα was the immune product whose serum level was most closely related to weight loss suggests that T lymphocyte IL-2 receptor upregulation, in addition to the acute-phase protein response, may influence weight loss. Reports that T lymphocytes from patients with advanced colorectal cancer are 'anergic' to *in vitro* challenge[27], and that patients with colorectal liver metastases have reduced cell-mediated immunity[28], appear inconsistent with these results. This association of T cell anergy, low serum IL-2 level and raised sIL2rα level has been reported previously in both cancer and chronic inflammatory disorders[29–31]. The findings are compatible with factors associated with an inflammatory (innate) immune response to colorectal cancer activating[32] a deficient cellular (acquired) response[33]. This combination of T cell anergy associated with IL-2 receptor upregulation can be produced experimentally[34] by alteration of the T cell receptor ligand using an antigenic peptide analogue on a functional antigen-presenting cell. Previous pharmacological strategies to reduce cytokine-related weight loss in cancer have focused on agents that reduce monocyte-related cytokines in the acute-phase protein response[21,35]. Agents that influence T lymphocyte IL-2 receptor release might also be beneficial.

Both tumour volume and the tumour marker serum CEA level correlated with weight loss, and serum CEA was the strongest predictor of weight loss in the regression analysis. This suggests either that the circulating levels of immune products measured did not accurately represent the immune products which influenced metabolism at the cellular level[36] or that tumour-related products also influenced weight loss by non-immunological mechanisms[35].

No significant differences in serum levels of hormones that influence metabolism were detected. It is possible that the effects of these hormones altered without a change in serum levels, but the present findings did not support a role for hormone-related metabolic changes in the weight loss produced by colorectal liver metastases. The lack of an association of plasma AST or ALT with weight loss suggests that reduced liver function from liver metastasis-related hepatocyte destruction was unlikely to explain the weight loss. This is consistent with the observation[8] that hepatic parenchymal volume is not reduced in patients with colorectal liver metastases.

In summary, significant weight loss from colorectal liver metastases required a large tumour volume. This weight loss was not explained by changes in diet, quality of life or hormones, but activation of the innate and incomplete activation of the acquired immune systems were likely to be involved. Additional non-immune-mediated tumour-related factors may also be important.

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Use of a unilateral pudendal thigh flap in the treatment of complex rectovaginal fistula

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Introduction

The treatment of rectovaginal fistula is based on its classification[1,2]. Usually a simple fistula can be treated successfully by a local repair procedure[1–3]. In local repair of a complex fistula, failure rates of 30–40 per cent have been reported[3], due mainly to the presence of abnormal, inflamed, infected and/or poorly vascularized surrounding tissue which prevents normal postoperative wound healing. Accordingly, the use of an abdominal or tissue transposition procedure is recommended for the treatment of complex fistulas.

In tissue transposition procedures a well vascularized pedicled flap is introduced between the rectum and the vagina. This paper describes a tissue transposition procedure, illustrated by two cases, in which a unilateral neurovascular pudendal thigh flap was used to correct a complex rectovaginal fistula.

Patients and methods

Two women who presented with a complex rectovaginal fistula were treated by use of a unilateral pudendal thigh flap. The technique consists of making an inversed T incision in the posterior vaginal wall across the orifice of the fistula. A vaginal flap is raised bilaterally, exposing the underlying rectovaginal septum and perineal body. The fistulous tract is excised and the rectal mucosa and muscle are closed in sequential order.

A horn-shaped flap is raised, centred on the crease of the groin, including skin, subcutaneous tissue, deep fascia of the thigh and epimysium of the adductor muscles and measuring approximately 15 × 6 cm. The posterior incision is taken to a depth of 1–1·5 cm, through dermis and subcutaneous tissue only, and then undermined posteriorly, parallel to the skin, for a distance of 4 cm. This results in a large flap borne on a subcutaneous pedicle containing the posterior labial arteries from the pudendal artery and the posterior labial branches from the pudendal nerve as well as the perineal rami of the posterior cutaneous nerve of the thigh. The flap is tunnelled under the labium majus and rotated in the defect between rectum and vagina (*Fig. 1*). All the tissue lying subcutaneously is

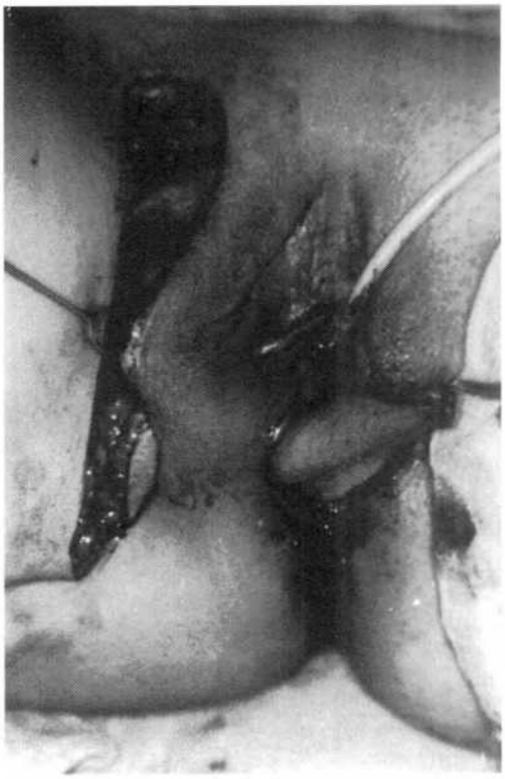

Fig. 1 Tunnelling and rotation of the neurovascular flap into the defect between rectum and vagina

de-epidermealized, and the vaginal wall is closed and attached to the flap with interrupted sutures.

Results

Two years after performing the flap procedure both patients have had no recurrence of the fistula. They have normal bowel function and continence with a normal sphincter mechanism. No dyspareunia has been reported.

Discussion

The neurovascular pudendal thigh flap has been described in the literature as a bilateral technique for vaginal and scrotal–penile reconstruction in congenital and acquired conditions[4,5].

The unilateral technique may be employed to repair difficult perineal wounds and complex fistulas. It prevents direct apposition of two suture lines and introduces well vascularized tissue into the area, restoring the normal anatomy and function of both vagina and anorectum. The flap is robust and sensate with a reliable blood and nerve supply[4]. The flap is raised with the deep fascia of the thigh and the epimysium of the adductor muscles, thereby creating an additional barrier that prevents possible damage to the neurovascular structures running in the flap[5]. There is little donor site morbidity with concealed scars. Long-term follow-up is essential to determine precise recurrence rates.

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Original article

Comparative study of two sites of colonic conduit placement in the treatment of constipation due to rectal evacuatory disorders

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Background: Chronic constipation may be treated by antegrade colonic irrigation via a colonic conduit.
Methods: Two alternative sites of colonic conduit construction were evaluated for their effect on the symptoms of 21 consecutive women with intractable constipation primarily due to rectal evacuatory disorders. The conduit was constructed in the sigmoid colon in the first 11 patients and in the transverse colon in the subsequent ten. Symptomatic outcome was evaluated clinically and by questionnaires, with a prospective quality of life assessment in the transverse group.
Results: During a median follow-up of 12 (range 6–60) months, reflux or stenosis necessitated revision or dilatation in six patients. Irrigation with a median of 1 3 (0 8–2·0) litres of water achieved evacuation in all patients. Improvements in abdominal pain and bloating were reported by seven of the ten patients in the transverse conduit group, but benefit was found in only three of 11 in the sigmoid group. There was no significant improvement in quality of life scores. In the medium term, seven patients retained a transverse conduit compared with three with a sigmoid conduit.
Conclusion: The transverse colonic conduit offers better relief from the symptoms of constipation due to rectal evacuatory dysfunction than the sigmoid conduit.

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Introduction

Chronic constipation is associated with distressing symptoms for which patients may seek surgical solutions when medication and biofeedback therapy[1] have failed. Retrograde enemas can help some patients with disordered evacuation[2], but they can cause complications[3] and complete evacuation cannot be achieved reliably. Patients with slow colonic transit may undergo subtotal colectomy and ileorectal anastomosis but up to one-half have continued symptoms or diarrhoea[4,5].

Antegrade colonic irrigation via an appendicostomy has been described as a therapy for incontinence and constipation in children and adults[6]. Despite technical modifications the appendicostomy is prone to stenosis, with reported revision rates of up to 50 per cent[7]. The use of an appendicostomy may be impractical in adults both because of stenosis and because up to half the women presenting with constipation have previously had an appendicectomy[8]. Tubularized caecum[9] or ileum[10] can be used to overcome the problem of an absent appendix but stenosis may still occur.

The colonic conduit provides a catheterizable channel leading from the skin to the colonic lumen which incorporates a full-thickness intussuscepted valve to prevent reflux[11]. When the technique was originally devised conduits were sited in the sigmoid colon[12], but latterly conduits have been constructed in the proximal transverse colon[13]. This study was designed to compare and contrast the results of these two conduit positions.

Patients and methods

Twenty-one women with constipation related to rectal evacuatory disorders and resistant to maximal medical therapy who underwent the previously described procedure of conduit formation[11] were studied. Eleven patients (median age 38 (range 26–47) years) who were treated during 1993–1995 were offered a sigmoid conduit. Subsequently ten patients (median age 48 (range 25–74) years) received a transverse conduit during 1994–1997.

Before operation all patients were fully assessed using radio-opaque marker colonic transit studies and evacuation proctography with integrated puborectalis electromyography (EMG) if anismus was suspected[14]. Four patients in the sigmoid and two in the transverse group were found to have coexistent segmental transit delays, and two patients with anismus in the sigmoid group and three in the transverse group had proved unresponsive to EMG-based biofeedback. Any anatomical abnormality of the rectum that was considered clinically significant was repaired at the same time as conduit construction. One patient in the sigmoid group and one in the transverse group had a large (greater than 3 cm in diameter) rectocoele repaired by a perineal approach and four patients (three in the transverse group) had a simultaneous sutured rectopexy for intrarectal intussusception.

The aetiology of constipation was frequently multifactorial, with documented psychological dysfunction in six cases (four sigmoid, two transverse). Symptom onset was temporally related to gynaecological surgery in 13 patients (six in the sigmoid group, seven in the transverse group). Three patients had previously had an abdominal rectopexy, of whom one was treated with a sigmoid conduit and two with a transverse conduit.

All patients were counselled carefully by members of the multidisciplinary team, and informed consent was obtained before operation. After surgery the patient was taught to intubate the conduit and perform antegrade irrigation with warm tap water. Patients were followed in the outpatient clinic, where standard questionnaires were used to record irrigation technique and to identify symptoms and complications. In addition all patients were contacted by post in 1997 and asked to complete a standard questionnaire assessing current bowel function, irrigation technique and symptoms of reflux, pain, bloating or incontinence.

The last eight patients having a transverse conduit were invited to participate in a prospective postal evaluation of quality of life before and at 6-month intervals after operation using the Nottingham Health Profile[15] and the Hospital Anxiety and Depression Scale[16].

Results

Median follow-up was 11 (range 4–60) months in the sigmoid group and 14 (range 6–48) months in the transverse group. Two transverse and one sigmoid conduit were excised within 1 year of operation because of persistent valvular reflux, and revision or dilatation for stenosis was needed in a further two patients in each group. One sigmoid conduit developed mesenteric fat necrosis which necessitated early excision and ileostomy formation.

In both groups irrigation was performed between four and seven times a week using a median of 1·3 (range 0·8–2·0) litres of warm water. In addition three patients in the sigmoid group and two in the transverse group intermittently used phosphate enema solutions per conduit. Irrigation took a median of 40 (range 10–60) min per irrigation, compared with the reported median of 60 (range 20–180) min per action spent evacuating before operation.

In the sigmoid group only one of the eight patients with preoperative abdominal pain and two of the seven with preoperative bloating obtained relief of symptoms. Consequently six patients in the sigmoid group underwent conduit excision and either colectomy and ileorectal anastomosis (performed in two patients with coexistent segmental transit delays) or an end ileostomy (four patients). Overall only three of the 11 patients in the sigmoid conduit group used the conduit successfully in the medium term.

Questionnaires in the transverse conduit group revealed that five of the seven women with preoperative abdominal pain and seven of the nine with preoperative bloating achieved symptomatic relief after operation. As a result seven of the ten patients in the transverse group continued to use the conduit and only one underwent conduit excision and ileostomy formation because of persistent abdominal pain.

Despite apparent symptomatic relief in the transverse group there was no overall improvement in Nottingham Health Profile quality of life scores. There was a trend towards improvement in the domain of emotional disturbance, where scores decreased from a median of 41 (range 10–63) to 4 (0–48) at latest follow-up. The conduit had no apparent effect on Hospital Anxiety and Depression scores, with anxiety levels remaining above the normal range both before and after operation.

Discussion

The small group size and non-randomized methodology limit the statistical power of this study, so comparative statistical analysis has been avoided. However, patients in both groups were women with similar aetiology and pathophysiological findings, and various comparisons between the two sites of conduit placement are useful.

There were a number of technical complications in both groups. Stenosis of the conduit orifice necessitated dilatation or revision in three patients, while significant valve reflux occurred in four. The incidence of both these complications appears to be comparable to or less than that reported in series of antegrade irrigation by appendicostomy or tubularized caecal flap[15,17]. Most series of appendicostomy have comprised children with incontinence, whereas the present series consisted of constipated adults. A direct comparison between the colonic conduits and published appendicostomy data is inappropriate. Whether the use of an appendicostomy or tubularized ileum or caecum would have produced a similar functional outcome to the transverse conduit is unknown, but could form the basis of a future randomized controlled trial.

The data are complicated by the fact that six patients had simultaneous interventions for rectocoele or rectal prolapse at the same time as conduit construction. Rectocoele is frequently found in constipated women but it may be secondary to the constipation[17], with rectocoele repair alone yielding disappointing results[18]. In the present series one large rectocoele was repaired in each group at the same time as conduit construction but five smaller rectocoeles were not repaired during transverse conduit surgery. All patients with a rectocoele, whether repaired or not, achieved a reduction in the preoperative symptoms, although one failed because of valve reflux. This suggests that correction of the underlying evacuatory disturbance by antegrade irrigation is more important than repair of the rectocoele itself.

Of the four patients who underwent rectopexy at the same time as conduit formation, only the three with a transverse conduit improved symptomatically. The small group size and heterogeneity of the patients renders it impossible to determine whether rectopexy alone would have sufficed, although these patients are still prone to constipation if they fail to irrigate adequately.

In this study the transverse colon appeared to be a superior site for conduit placement, with only three of 11 patients in the sigmoid group but seven of ten in the transverse group achieving success in the medium term. Contrary to earlier reports of successful use of the sigmoid conduit[12], antegrade irrigation of the rectosigmoid alone is ineffective, and symptomatic relief is more likely to be achieved with a transverse conduit.

Why complete left-sided evacuation should be more effective in providing symptom relief is unknown, although scintigraphic studies[19] suggest that stool within the ascending and the transverse colon as well as that within the rectosigmoid is evacuated during defecation in both constipated and normal people. Irrigation via the proximal colon may therefore restore a more physiological defaecatory mechanism.

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Original article

Controlled digital anal dilatation under total neuromuscular blockade for chronic anal fissure: a justifiable procedure

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Background: There is widespread antipathy to digital dilatation of the anus (DDA) for medically resistant anal fissure. A retrospective study was therefore undertaken to test the validity of the criticism of this technique.

Methods: Some 273 patients who underwent DDA for fissure between November 1982 and July 1997 were sent a questionnaire and/or telephoned. Those with impaired control were offered investigation. In addition, routine clinic follow-up data were scrutinized in the 302 available notes of the 307 patients who had undergone DDA for fissure to determine its efficacy.

Results: Some 241 patients (88·3 per cent) were contacted successfully a median of 7·8 years after operation. Follow-up records showed the fissure to have healed in 89·1 per cent of 302 patients. No patient was rendered incontinent. Fifteen patients indicated persistently impaired control in the questionnaire, nine (3·8 per cent) as a result of the DDA and six preceding it. All 23 patients who had experienced either temporary or permanent impairment, whether or not pre-existing, were invited to attend for ultrasonography and manometric measurements, of whom 18 accepted. No sphincteric fragmentation was seen, and resting and squeeze pressures did not differ from normal.

Conclusion: A single DDA appears to heal 89 per cent of chronic anal fissures. Consequent impairment of control is infrequent and minor if the procedure is performed carefully and with the patient paralysed.

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Introduction

Digital dilatation of the anus (DDA) can cause severe sphincteric damage. Manometric and ultrasonographic studies have documented the injuries sustained in patients referred to a tertiary referral centre[1,2], and one retrospective review of 100 patients treated by stretching revealed an unacceptable rate of sphincter impairment[3]. These publications have understandably affected the prevailing perception of the propriety of a method criticized in any event for its lack of accuracy and control. The Royal College of Surgeons of England's recent Comparative Audit finding that members of the Association of Coloproctology of Great Britain and Ireland were significantly less likely to use DDA for chronic anal fissure than non-members – lateral internal sphincterotomy (LIS) being preferred – was therefore unsurprising[4].

However, the questionnaire by McDonald *et al.*[3] was returned by only 55 per cent of the patients studied, and these patients had undergone stretching for a variety of conditions. A disturbingly high level (35 per cent) of permanent loss of control, including faecal incontinence, was also discovered in Khubchandani and Reed's very much larger study after LIS[5].

That there is in fact nothing in the literature on the subject to persuade surgeons to abandon one method in favour of the other is illustrated in *Fig. 1*, which displays the results of all published studies over the past 30 years in which functional outcome has been reported (sometimes only in the discussion, without evidence of its being formally sought) after LIS or DDA. Despite the discrepancy in study size and the drawbacks of comparison between retrospective series, it is at least apparent that neither method is definitely superior; several prospective randomized trials have produced similar results (*Fig. 2*)[3,5–34].

In the event of failure of glyceryl trinitrate ointment to heal chronic anal fissure, one or other method will be needed for the foreseeable future. In the light, therefore, of the possible outright condemnation of DDA, a study was undertaken of patients treated by DDA, with the aims of discovering whether anal stretching in fact deserves its

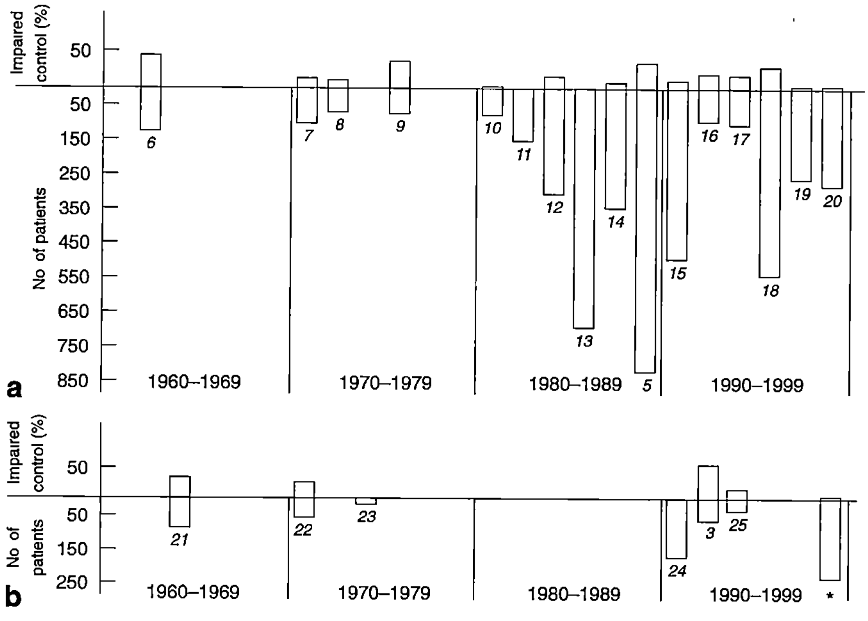

Fig. 1 Bar chart depicting the numbers of patients and percentage with impaired control in studies reporting functional results after **a** lateral internal sphincterotomy and **b** digital dilation of the anus. Reference numbers are shown below bars; *present study

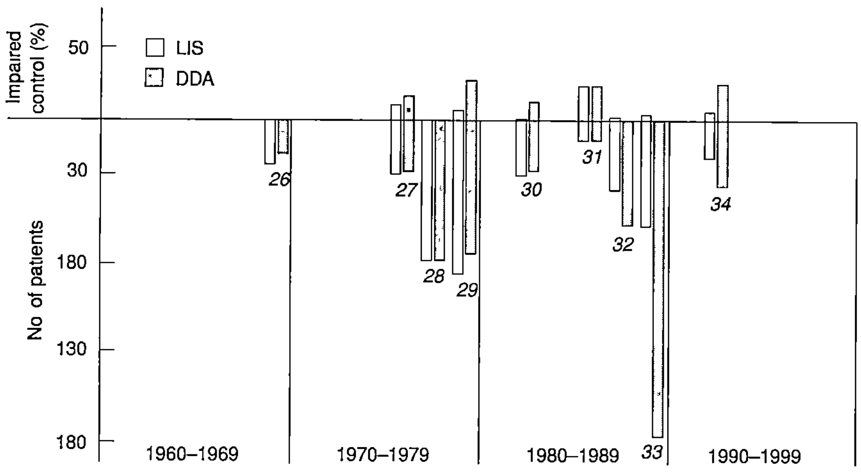

Fig. 2 Bar chart depicting the numbers of patients and percentage with impaired control in randomized comparative trials of lateral internal sphincterotomy (LIS) and digital dilation of the anus (DDA). Reference numbers are shown below bars

bad reputation and of adding to the much smaller published knowledge of the outcome of DDA.

Patients and methods

The notes of the 399 patients who had undergone DDA under the care of a single surgeon from November 1982 to July 1997 were studied and patients who had had DDA as primary treatment for fissure were identified. Twenty-three had died, 92 had had DDA for another indication and 11 had been treated previously for fissure elsewhere. The study group therefore comprised 273 patients. In each, DDA had been recommended after the failure of conservative management of chronic anal fissure. The sex ratio (M : F) was 1·05 and the median age of the patients was 40 years.

Digital dilation of the anus

The procedure was performed with the patient under general anaesthesia and lying in the left lateral position. In addition patients were usually paralysed with suxamethonium (total neuromuscular blockade) during the procedure to prevent inadvertent contraction of the external sphincter and potential damage during dilation.

Digital dilation was performed by controlled stretching evenly distributed around the anal circumference by rotating the hands, and continued until it was perceived that no further reasonably achieved increase would occur. This required differing amounts of force according to the toughness of the internal sphincter. Trainees carried out DDA unsupervised when they had demonstrated their grasp of the technique.

Data collection

The questionnaire enquired about current, preoperative and immediate postoperative control, and about fissure recurrence. Follow-up was improved by telephoning non-responders. The surgeon's grade was recorded together with additional procedures, type of anaesthetic, postoperative complications, requirement for further surgery and obstetric history. Subgroup analysis sought to detect whether the surgeon's grade influenced the outcome, and any ill effect of reoperation or of obstetric history.

Analysis of functional impairment

Patients who had indicated any temporary, permanent or pre-existing loss of anal control were invited for investigation, and their impairment was scored according to Browning and Parks' classification (*Table 1*)[35]. Anal endosonography (AES) was performed using a 10-MHz endoprobe ultrasound scanner (Brel & Kjaer, Naerum, Denmark) and anal manometry with a solid-state anorectal catheter (Gaeltec, Dunvegin, UK) linked to a medical PC Polygraf (Synectics, Stockholm, Sweden). The mean of three separate readings was recorded for steady-state and maximal squeeze.

Results

The questionnaire was returned by the patient or completed over the telephone by one of the authors in 241 patients (88·3 per cent), at a median follow-up of 7·8 years. Some 53·5 per cent of these had had primary treatment by the senior author and the rest by trainees on the firm.

The hospital records were available for 302 of the 307 patients who had undergone DDA for fissure and provide the follow-up data (from the routine 2-month postoperative appointment entry) from which healing rates were deduced.

Table 1 Browning and Parks' classification[35]

Category A	Normal continence except an occasional lack of flatus control
Category B	Regular incontinence of flatus with usual continence of solid and liquid stool
Category C	Intermittent small volume faecal leakage with usual incontinence of flatus but acceptable continence of solid stool
Category D	Gross incontinence of solid and liquid stool

Fissure healing

Table 2 displays the requirement for further surgery after a single DDA by both consultant and trainees as determined from the follow-up clinic findings and other data in the patients' records. The apparent overall success rate was 89·1 per cent, based on data from notes of 302 patients.

Persistent or recurrent fissure was managed by a further DDA in 24 patients and LIS in five. The other four patients were assumed to have persistence of fissuring on the basis of their requirement for further anal surgery, either haemorrhoidectomy (one patient) or fistulotomy (three).

Impairment of control

Table 3 shows the outcome according to the Browning and Parks' classification. Some 23 patients in the study group of 241 reported impaired control after DDA. However, six of them indicated that control had been similarly impaired before DDA (four B, two C) and so have been excluded from *Table 3*. Including them would give an impairment rate of 3·7 and 2·5 per cent respectively for Browning and Parks' categories B and C. The other eight patients reported that impairment of control after DDA was temporary and were therefore designated category A.

Overall, persisting impairment of control therefore afflicted 3·8 per cent of patients who had been untroubled before operation. If the six patients who indicated similar preoperative impairment are considered to have misunderstood the questionnaire and are believed to have suffered from the procedure, then 6·2 per cent of patients

Table 2 Healing of fissure by single digital dilation of the anus

	No. of patients	No requiring further surgery
Consultant	163	9 (5·5)
Trainee	139	24 (17·3)
Total	302	33 (10·9)

Values in parentheses are percentages

Table 3 Impaired control after digital dilation of the anus in 235 patients reporting normal preoperative control

Browning and Parks' category	No. of patients
A	226 (96·2)
B	5 (2·1)
C	4 (1·7)

Values in parentheses are percentages

Table 4 Factors effecting continence after digital dilation of the anus

	No of patients	No. of patients with impaired control*
Consultant	129	7 (5·4)
Trainee	112	9 (8·0)
Single DDA	211	12 (5·7)
Reoperation	30	4 (13)

Values in parentheses are percentages. *Category B or C in Browning and Parks' classification[35]. Included in this table are the six patients who indicated that they had experienced similar impairment of control before digital dilation of the anus (DDA)

can be said to have had impairment of control as a result of DDA. Of the six patients in category C one had ulcerative colitis, one perianal dermatitis and two others declined the offer of investigation. No patient was incontinent of faeces. Two patients suffered urgency, of whom only one wore a pad (the patient with colitis).

All 23 patients who had reported impairment, whether transient or permanent, pre-existing or not, were invited to undergo investigation and 18 accepted (ten men, eight women; median age 50 years). Mean resting anal pressure was 90·1 (range 53 6–127·8) cmH_2O and maximal squeeze pressure was 185·1 (range 85 7–340·9) cmH_2O. AES demonstrated four to be normal, eight to show minor internal sphincter changes (thinning in five and thickening in three) and six to have a superficial focal defect. An associated superficial external anal sphincter defect was suggested by AES in three of the last group and one of the second, but three such defects were anterolateral in parous women.

The obstetric history was recorded in 96 of the 116 women in the study. Some 75 of them (78 per cent) had had a vaginal delivery. All six of the women reporting persistently impaired control had had vaginal deliveries (average two each) and three indicated that the same anal control impairment had existed before DDA.

Subgroup analysis sought differences in outcome between consultant and trainee, and differences in impairment resulting from repeated DDA (*Table 4*).

Discussion

Some of the study results depicted in *Fig. 1* are difficult to interpret. In the paper by Vafai and Mann[13] reporting the outcome of LIS performed in Iran, for instance, there is no indication of follow-up time or achievement and no mention of functional data collection in either the methods or results section; the figure of 1 per cent for impairment of control appears, *inter alia*, in the discussion. The stated purpose of the study by Khubchandani and Reed[5], in contrast, was to determine the proportion of patients undergoing LIS who were adversely affected. The explanation for the substantial published differences illustrated in *Fig. 1* can partly be attributed both to the definitions used by the investigators and the vigour with which the information was sought. This fact notwithstanding, careful studies have shown that LIS has a deleterious effect on anal sphincteric function in a proportion of patients, as many as 35·1 per cent in one large study[5] and 30·3 per cent in another[18].

The alternative, DDA, has two undeniable disadvantages; it is difficult to define and therefore to teach, and excessive force, which is difficult to judge, can have serious consequences. The slightly greater number requiring further surgery after DDA by an unsupervised trainee (17·3 *versus* 5·5 per cent) probably reflects these drawbacks. Lestar *et al.*[36] used a restraining ligature around the surgeon's fingers and Sohn *et al.*[24] employed a balloon. However, both the force and magnitude of the stretch have to be tailored to the patient so such standardization, although laudable in aim, seems flawed.

Total neuromuscular blockade allows an unencumbered assessment and stretching of the internal sphincter and may, in preventing counteraction to an inadvertently contracting external sphincter, eliminate the possibility of its damage.

Both lowered anal pressure and severe structural damage may follow DDA[1,2], but even the group of 18 patients with impaired control who presented for investigation were found to have resting and squeeze pressures similar to those of symptomless volunteers in a Finnish study[37], and none had sustained severe injury to the internal sphincter. In eight of them the sphincter was either ultrasonographically normal or thickened and five had minor eccentric thinning.

In conclusion, while the potential for severe and irreparable damage by DDA must neither be forgotten nor underestimated, LIS results in a permanent breach not seen after stretching and has drawbacks too. The present study is the biggest investigation of the functional outcome of DDA yet published and has the longest follow-up, and suggests that fissure can be cured by stretching which, done with care and perhaps total neuromuscular blockade, can achieve a functional morbidity comparable to the functional results of LIS reported in the literature[5–34].

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Comparison of open posterior *versus* transperitoneal laparoscopic adrenalectomy

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Background: This study reviewed the results of initial experiences of open posterior adrenalectomy and transperitoneal laparoscopic adrenalectomy in 46 patients.
Methods: Twenty-three adrenalectomies were performed using the open posterior approach. Detailed records of the patients' operative and postoperative progress were compared with those of the first 36 laparoscopic adrenalectomies undertaken for a similar range of conditions.
Results: Conversion to laparotomy was necessary in one of 23 open posterior adrenalectomies and five of 36 laparoscopic adrenalectomies. The mean operating time for laparoscopic unilateral adrenalectomy was nearly double that for open surgery (158 *versus* 85 min). Postoperative complications occurred more frequently in the open adrenalectomy series (12 of 23 *versus* two of 36) but one late unexplained death followed bilateral laparoscopic adrenalectomy. A mean reduction in hospital stay of 5 days was recorded after laparoscopic adrenalectomy (range 2–5 days for laparoscopic *versus* 6–11 days for open operation).
Conclusion: Transperitoneal laparoscopic adrenalectomy was attended by a lower morbidity rate than open adrenalectomy and patients were discharged from hospital more quickly.

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Introduction

In the face of rapidly advancing endosurgical technology there is understandable reluctance to deny patients the possible advantages of minimally invasive surgery. Randomized trials comparing conventional open operation and endoscopic surgery are unlikely to be undertaken, especially for rare adrenal lesions when the morbidity associated with open operation remains high. Since it was first performed in February 1992[1], reports from around the world have indicated that laparoscopic adrenalectomy for both functioning and non-functioning tumours can be undertaken safely[2–5]. Consensus has not yet been reached as to which pathologies, size of adrenal tumour or patient characteristics render an individual suitable for endoscopic surgery. This study reports the results of a non-randomized series of 46 patients who underwent open posterior or transperitoneal laparoscopic adrenalectomy. Comparison is made between the two groups, which represent an initial experience for both surgical approaches.

Patients and methods

Between September 1989 and November 1994, 23 adrenalectomies were attempted by N.E.D using the Hugh Young posterior approach. During this interval, patients with an adrenal mass larger than 5 cm, or a suspected/confirmed malignant tumour, underwent surgery via the anterior open approach. Between November 1994 and July 1997, 36 laparoscopic adrenalectomies were attempted by both authors working together in Oxford and Sheffield. The only patients not offered endoscopic adrenalectomy in the second time interval were those with a bulky tumour (more than 10 cm diameter), suspicion of malignant change or patients with a significant history of thromboembolic disorder in whom a prolonged increase in intra-abdominal pressure secondary to pneumoperitoneum might have increased the risks. Three patients were excluded on these criteria. Open adrenalectomy was performed on 15 patients (11 women, four men), of mean age 44 (range 24–62) years (*Table 1*). Thirty-one patients underwent laparoscopic adrenalectomy (18 women, 13

Table 1 Details of 15 patients who had open posterior adrenalectomy from 1989 to 1994

Diagnosis	No. of patients	Maximum diameter (mm)*	Side (R : L)	Operating time (min)†	Blood loss (ml)†	Inpatient stay (days)
Virilizing adenoma	1	22	0 : 1	95	300	11
Cushing's syndrome (adenoma/hyperplasia)	4	29 (20–40)	3 : 2	90 (85–110)	400 (200–500)	6–8
Cushing's disease/ ectopic ACTH	7	39 (32–50)	Bilateral	130 (80–155)	600 (500–2000)	8–11
Conn's syndrome (adenoma)	2	12 (10–15)	1 : 1	75 (60–90)	150 (100–200)	6–8
Phaeochromocytoma	1‡	50	0 : 1	—	—	—

Values are *mean (range) or †median (range). ‡Conversion to open procedure. ACTH, adrenocorticotrophic hormone

Table 2 Details of 31 patients who had transperitoneal laparoscopic adrenalectomy from 1994 to 1997

Diagnosis	No. of patients	Maximum diameter (mm)*	Side (R : L)	Operating time (min)†	Blood loss (ml)†	Inpatient stay (days)
Virilizing adenoma	1	25	0 : 1	120	50	2
Cushing's syndrome (adenoma/hyperplasia)	5	41	3 : 3	157 (90–210)	150 (50–400)	3–5
Cushing's disease/ ectopic ACTH	6‡	36 (25–75)	3 : 4	177 (120–225)	225 (75–500)	2–4
Conn's syndrome (adenoma)	5	16 (10–20)	2 : 3	140 (90–180)	20 (0–150)	2–4
Incidentaloma	1	50	1 : 0	120	200	2
Phaeochromocytoma	13§	50 (15–82)	4 . 8	178 (105–315)	275 (50–500)	2–4

Values are *mean (range) or †median (range) The operation was converted to an open procedure in ‡two and §one patients; operating time, blood loss and inpatient stay were excluded for these patients. ACTH, adrenocorticotrophic hormone

men), of mean age 40 (range 5–84) years (*Table 2*). The largest adrenal tumour removed via the posterior route was 5 cm in diameter whereas four patients undergoing laparoscopic adrenalectomy had tumours 7–9 cm in diameter; all were phaeochromocytomas.

Surgical technique

Open posterior adrenalectomy was performed using the approach popularized by Young[6]. The traditional vertical hockey stick incision was favoured as it provided optimal access. The adrenal vein and arteries were divided between clips. Suction drainage was used selectively.

The technique adopted for transperitoneal laparoscopic adrenalectomy was described by Gagner and colleagues[1] with subsequent modification[7]. Patients were positioned in the lateral decubitus position and the trunk tilted approximately 30° off the centre line with the table broken to open up the thoracolumbar angle. Ten-millimetre working ports were used exclusively (except in the only child, in whom 5-mm ports were used). Experience established that it was more efficient to site all ports close to the costal margin, four on the right and three or four on the left. The use of suction drains was selective. Fascial closure was performed with the operating table returned to the neutral position.

Patients with Cushing's syndrome received perioperative and postoperative hydrocortisone, the dose of which depended on the severity and duration of disease. Metyrapone was given before operation to some severely affected patients with Cushing's syndrome in an attempt to block cortisol synthesis. All patients in both series were fitted with graduated elastic compression stockings before operation; these were worn for the duration of hospital stay. Intraoperative intermittent calf compression was used and all patients were given subcutaneous heparin on induction of anaesthesia and regularly until discharge. Patients in both series with phaeochromocytoma were stabilized before operation with α-blockers; the dose was titrated until the blood pressure was controlled. In some patients, once adequate α blockade was established, a β-blocker was given to reduce the risk of tachydysrrhythmia. Patients with a Conn's tumour all received treatment before operation to normalize blood pressure and plasma potassium level.

The operating time was recorded in open operations from skin incision to completion of skin closure, and in laparoscopic operations from insertion of the Veress needle for peritoneal insufflation to skin closure. Blood loss was estimated by swab weight and/or suction volume. Complications that occurred within 30 days of surgery were documented. All patients had routine follow-up. Analgesic requirements were not compared for the two series as the pain relief strategy changed in both centres during the study. Time to discharge was defined as the number of hours that elapsed after the patient had returned to the surgical ward and was fit to return home or transfer to a medical ward (if there was a need to monitor cortisol levels or measure other hormone levels).

Results

Open posterior adrenalectomy was completed successfully in 22 of the 23 operations performed. The single unsuccessful procedure requiring conversion to laparotomy involved a left-sided 50 × 40-mm phaeochromocytoma with extensive neovascularization that could not be controlled safely through the limited posterior access. Laparoscopic adrenalectomy was completed successfully in 31 of 36 operations. The majority of the conversions occurred early in the series (patients 4, 5, 18, 19 and 21) and all but one had end-stage Cushing's disease, i.e. failed pituitary surgery with very fragile tissues and significant truncal obesity. In these patients venous oozing obscured the view, and suction irrigator failure compounded the problem in operations 18 and 19. After open adrenalectomy the blood loss was significant in two of the 22 patients; each required 2 units of blood. Two of the 31 successful laparoscopic adrenalectomies also required transfusion of 2 units. The remainder had insignificant blood loss; suction drainage was rarely used.

The mean operating time for open unilateral adrenalectomy was 85 (range 60–110) min. Laparoscopic adrenalectomy was completed in a mean of 158 (range 90–315) min. Left-sided laparoscopic adrenalectomy took 16 min longer on average to complete than that on the right. Operating time did reduce with experience (*Fig. 1*) but phaeochromocytomas remained the most time consuming tumours to remove laparoscopically. Bilateral adrenalectomy took a mean 119 min to perform as an open procedure and 386 min laparoscopically. This included the time taken to change sides and reposition the patient where required. There was no morbidity with regard to medical preparation in either series but two of the 13 patients with phaeochromocytoma who underwent laparoscopic adrenalectomy required additional pharmacological therapy on induction and during operation to control hypertension.

Perioperative complications after open adrenalectomy included wound infection (three patients), chest infection (five), pressure sore (one), renal failure (one) and urinary infection (two). Perioperative complications after laparoscopic adrenalectomy were confined to one wound infection and one port-site hernia. This hernia occurred on the fourth day after operation and could be explained by a failure to unbreak the table before wound closure. At re-exploration, performed under local anaesthetic, the fascial suture was found to be intact, but the wound edges had not been approximated at initial closure. One patient who had bilateral laparoscopic adrenalectomy for end-stage Cushing's disease died at home on the eighth day after operation having had an uncomplicated hospital stay. At autopsy, no cause for death was found; specifically excluded were secondary haemorrhage at the operation sites and pulmonary embolus. Mean hospital stay after open surgery was 8·5 (range 6–11) days and after laparoscopic surgery 3·5 (range 2–5) days.

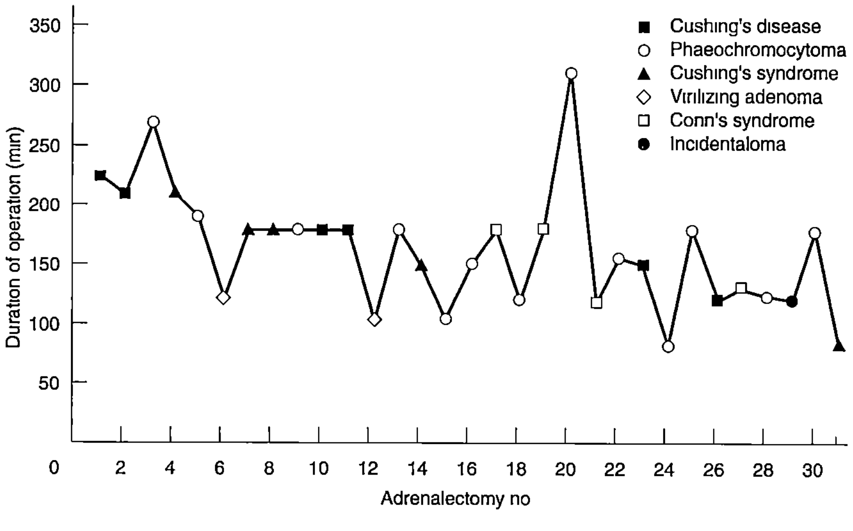

Fig. 1 Duration of operation of 31 consecutive laparoscopic adrenalectomies

The preoperative diagnosis was confirmed histologically in all patients except one in whom a phaeochromocytoma was validated biochemically, suspected to be in the left adrenal on computed tomography, but without uptake on [^{131}I]*m*-iodobenzylguanidine scintigraphy. The resected adrenal revealed a 1·5-cm diameter cortical adenoma but no medullary lesion. Nevertheless this patient now has normal catecholamine secretion and is clinically well. The single incidentaloma was a cortical adenoma with no evidence of malignant change.

The long-term benefit for patients in both series is still under review. No patient who underwent bilateral adrenalectomy for Cushing's disease or Cushing's syndrome has evidence of residual functioning adrenocortical tissue. No patient who had surgery for phaeochromocytoma requires antihypertensive therapy. The child with a virilizing adenoma now has normal height and weight velocity for her age.

Discussion

The aim of this study was to compare open posterior adrenalectomy and transperitoneal laparoscopic adrenalectomy. Elements of bias were unavoidable. First, the two series were consecutive and therefore not matched for age, sex or pathology. Patients with tumours larger than 5 cm were excluded from the posterior approach whereas there was no size limitation in the laparoscopic series. The open posterior adrenalectomies were performed by a single consultant surgeon and represent an initial learning curve for adrenalectomy performed by this approach. In contrast, the laparoscopic adrenalectomies were undertaken by two consultants who, while having substantial laparoscopic surgical experience, had no previous experience of laparoscopic adrenalectomy. The 36 attempted laparoscopic adrenalectomies represent two combined learning curves for this approach. Both surgeons had experience of open adrenalectomy performed by the anterior approach. Comparisons nevertheless are valid, since the mean patient age and range of adrenal pathologies were similar.

While both procedures were safe and attended by minimal blood loss, a sudden unexplained postoperative death did occur after laparoscopic surgery. Although post-mortem examination did not reveal evidence of myocardial ischaemia, haemorrhage or pulmonary embolus, an Addisonian crisis cannot be excluded as the cause of death. The importance of education for patients on the need for steroid medication should be emphasized after unilateral or bilateral adrenalectomy for hypercortisolaemic disorders. The greater proportion of patients with Cushing's syndrome/disease who had open surgery compared with laparoscopic surgery may have contributed to the relative complication rates. Nevertheless the low morbidity in the 11 patients with Cushing's disease/syndrome who had laparoscopic surgery is an important finding.

Preoperative positioning of the patient before open posterior or laparoscopic adrenal surgery is time consuming. For this reason the timing of the procedure commenced with the skin incision or insertion of the Veress needle. Operating time was approximately double for laparoscopic adrenalectomy. This may be partly explained by a steeper learning curve with the laparoscopic procedure. In initial cases, difficulties with specimen retrieval, particularly at left adrenalectomy when only three ports were used, contributed to a prolonged operation. This can be avoided, albeit at greater cost, if a specimen retrieval pouch is used which allows 'one-handed' retrieval.

The conversion rate in the laparoscopic series appeared high; however, all but one patient had Cushing's disease. Such patients are obese, have fragile tissues and bleed easily; the adrenals are not always enlarged. Patients with Cushing's disease present a severe test to the laparoscopic technique particularly early in a learning curve. With more experience, the authors no longer attempt to visualize the adrenal glands in these patients but simply remove the glands encased in periadrenal fat, avoiding many of the technical problems stated previously, in addition to the risk of gland fracture, a potential cause of recurrent hypercortisolism.

Although no attempt was made in this study to compare postoperative pain, patients became mobile more quickly after laparoscopic adrenalectomy and were discharged from hospital a mean 5 days earlier. Others[8–10] have reported a significant reduction in postoperative analgesic requirement after lapararoscopic adrenalectomy. Most large hospitals in developed countries have now made the necessary capital investment in endoscopic surgical equipment. The potential increased cost associated with laparoscopic adrenalectomy compared with conventional open surgery can be offset by lower morbidity and a reduction in bed occupancy.

This report confirms that adrenal tumours of varied pathology can be removed safely laparoscopically. During the learning curve, conversion to an open approach is more likely in patients with longstanding hypercortisolism, yet these are the patients who can benefit most by being spared rib resection and an extensive muscle-cutting incision.

It has been suggested that removal of a Conn's tumour by the posterior route provides the benchmark by which laparoscopic adrenalectomy can be judged[11]. There were only five such cases in this series; the surgery was straightforward and with no associated complications. The mean operating time was 140 min and mean time to discharge from hospital 3 days. This compares with the self-styled benchmark series[11] in which the mean operating time was 200 min, 15 per cent of patients had significant morbidity and mean time to discharge of 4·4 days was 1·4 days longer than in this series.

Although hospital stay was shorter in the laparoscopic group it is clear that there are factors other than the surgical approach that may contribute. Over the interval of the study, pressures from within the medical community and sources of external funding have resulted in reduced duration of hospital stay for many surgical procedures. Nevertheless the mean operative stay for the open and laparoscopic groups in this study was equivalent to that of other groups[8–10,12–16], who reported a duration of stay ranging from 5·7 to 7 9 days for open surgery and 3–4·1 days for laparoscopic adrenalectomy.

In this sequential review transperitoneal laparoscopic adrenalectomy was attended by lower morbidity than open adrenalectomy and patients were discharged from hospital more quickly. The length of stay after laparoscopic surgery may further decrease with greater experience[17]. Additional advantages of the laparoscopic procedure include the avoidance of an extensive, painful and disfiguring muscle-cutting scar.

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Original article

Epidemiology of Warthin's tumour of the parotid gland in an Asian population

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Background: Recent studies have documented a number of changing demographic features in the occurrence of Warthin's tumour (adenolymphoma) of the parotid gland. In order to analyse its epidemiology in an Asian population, a retrospective study was performed on all parotid neoplasms ($n = 289$) operated on between 1988 and 1998.

Patients and methods: A total of 209 consecutive patients were selected for study, 136 with pleomorphic adenomas (one bilateral) and 73 with Warthin's tumours (seven bilateral). Patients were analysed with regard to tumour incidence, age, sex and race. Smoking as an aetiological factor in the development of Warthin's tumour was also studied.

Results: Warthin's tumour formed 25 per cent of parotid tumours and its ratio to pleomorphic adenomas was 1 : 1·9. Multicentricity was found in 14 patients (19 per cent). The male : female ratio for Warthin's tumours was 4·6 : 1. The proportion of Warthin's tumours did not show any increasing trend relative to pleomorphic adenomas. The racial distribution of Warthin's tumours showed an increased incidence among Chinese and a reduced incidence among Malays and Indians. The adjusted odds ratio for sex and age favouring an association between smoking and Warthin's tumour was 39·5 (95 per cent confidence interval 10·5–149·0; $P < 0·0001$).

Conclusion: The incidence of Warthin's tumour is considerable among Asians although there is still male predominance. There is no rising incidence of Warthin's tumour; the trend parallels the declining smoking rate in the population. The lower incidence among ethnic groups with dark skin seems to suggest concomitant genetic factors other than environmental factors alone in histogenesis. Smokers have a 40-fold greater risk than non-smokers of developing a Warthin's tumour.

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Introduction

Warthin's tumour has generally been regarded as the second most common benign tumour of the parotid gland after pleomorphic adenoma[1]. It occurs largely as a disease of middle aged and elderly men. Recent studies have documented a number of changing demographic features in the occurrence of this tumour. Investigators have described both an absolute increase in the incidence of this tumour[2–5] as well as a relative increase in its incidence compared with that of pleomorphic adenoma[4,5]. The incidence among women is also reportedly rising and the male predominance of this tumour has apparently declined[6–11]. Attempts to explain these findings have focused on smoking as a possible aetiological factor in the development of Warthin's tumour.

Many of these data are now over a decade old and are generally descriptive in nature. Furthermore, the experience of the West, in what is predominantly a Caucasian population, has been reported previously. In order to analyse the epidemiology of Warthin's tumour in an Asian population, as well as to study smoking as a risk factor in its development, a retrospective study of all parotidectomies performed by the unit was conducted.

Patients and methods

Between July 1988 and August 1998, 360 consecutive parotidectomies were performed on 345 patients (15 were bilateral). For the purpose of the study, consecutive patients with Warthin's tumour or pleomorphic adenomas were selected from 289 patients with parotid neoplasm.

All the patients had undergone either superficial or total parotidectomy in the 10 years of study.

All the patients' medical records were reviewed to ascertain age, sex, race, histopathological diagnosis and smoking history. Missing information with regard to smoking was obtained through telephone interview. Patients were divided into two groups according to histopathological diagnosis of Warthin's tumour or pleomorphic adenoma; each group was analysed with regard to relative incidence, age at time of presentation, and sex and race distribution.

For the analysis of smoking as a risk factor in the development of Warthin's tumours, a case–control study was performed using patients with Warthin's tumours as cases and patients with pleomorphic adenomas as controls. There has been no documentation of any association between smoking and the development of pleomorphic adenoma[12]. A positive smoking history was defined as 10 pack-years (consumption of one pack of 20 cigarettes each day for 10 years or more). An odds ratio was calculated. Statistical analysis was performed using the logistic regression model and χ^2 test for significance.

Results

There were 80 tumours from 73 consecutive patients (seven bilateral) with Warthin's tumours of the parotid gland. Within the same period of time, 137 pleomorphic adenomas were removed from 136 patients (one bilateral). Pleomorphic adenoma was the commonest parotid tumour with a ratio of 1·9 : 1 to Warthin's tumour (*Fig. 1*). Histologically, 14 patients (19 per cent) had multiple foci of Warthin's tumour (12 had two foci; two had three foci). The rate of bilateral Warthin's tumour was 10 per cent and six of seven patients had synchronous lesions.

The incidence of Warthin's tumour and pleomorphic adenoma, expressed as a proportion of the total number of parotid tumours in each year of study, is shown in *Fig. 2*. While pleomorphic adenoma seemed to show a slow rising trend over the last few years, the incidence of Warthin's tumour did not rise relative to the former.

The male : female ratio for Warthin's tumours and pleomorphic adenomas was 4·6 : 1 (60 *versus* 13) and 1 : 1·4 (56 *versus* 80) respectively. The median age at presentation was 61 (range 34–81) years for Warthin's tumour and 42 (range 14–77) years for pleomorphic adenoma. The racial distribution of Warthin's tumours showed an increased incidence among Chinese and a reduced incidence among Malays and Indians (*Table 1*). There were no Indian patients with Warthin's tumours in this series.

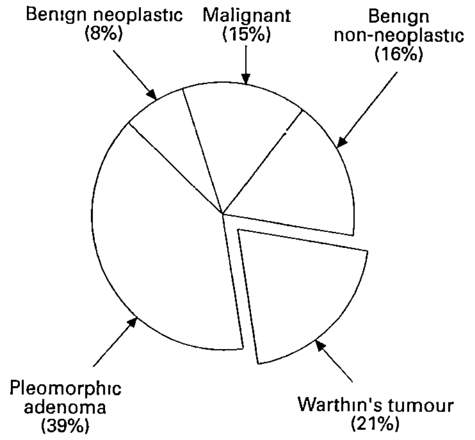

Fig. 1 Distribution, based on tumour histopathology, of 345 patients who underwent parotidectomy. Warthin's tumour formed 25 per cent of all parotid tumours (26 per cent of epithelial neoplasms)

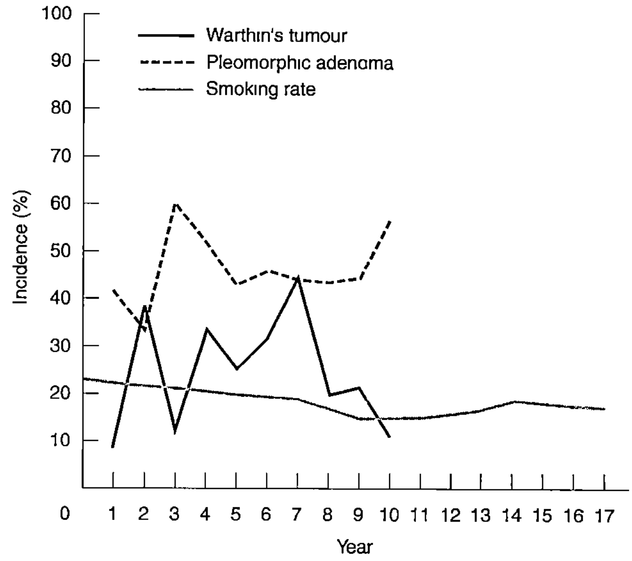

Fig. 2 Annual incidence rates of Warthin's tumour and pleomorphic adenomas operated between 1988 and 1998 expressed as a percentage of all parotid tumours, and prevalence of smoking among the population from 1977 to 1995. The 'Year' axis for smoking rate is a decade lag time behind the study period to enable the effects of any change in the prevalence rate to be captured in the annual incidence of parotid tumours

Of the 73 patients with Warthin's tumours, information regarding smoking was available in 70. In this group, 58 (83 per cent) of 70 were smokers. Of the 136 patients with pleomorphic adenomas, information regarding smoking

Table 1 Distribution of parotid gland tumours and prevalence of smoking by racial group

	Pleomorphic adenoma (n = 136)	Warthin's tumour (n = 73)	Population in 1990[13] (n = 2·3 million)	Annual referrals*	Smoking rate in 1995[14]
Chinese	112 (82·3)	66 (90)	(77·7)	(78·3)	(16·1)
Malay	15 (11·0)	4 (5)	(14·1)	(8·9)	(25·5)
Indian	4 (2·9)	0 (0)	(7·1)	(7·4)	(17·2)
Others	5 (3·7)	3 (4)	(1·1)	(4·9)	–

Values in parentheses are percentages. *New annual referrals made to the unit for all general surgical consultations, 1992–1998

was available in 133. Only 14 (11 per cent) of 133 patients in this control group were smokers. The odds ratio for the incidence of Warthin's tumour among smokers compared with non-smokers was 41·1 (95 per cent confidence interval 17·9–94·4; $P < 0.0001$). To adjust for sex and age, which are possible confounding factors, these variables were added to a logistic regression model containing smoking. This yielded an adjusted odds ratio of 39·5 (95 per cent confidence interval 10·5–149·0; $P < 0.0001$). Interaction terms were fitted to the model to look for effect modification. No significant effect modification by sex ($P = 0.38$) or age ($P = 0.41$) was detected.

Discussion

The true incidence of Warthin's tumour will not be realized for several reasons. First, as it is a benign tumour, reporting in a cancer registry is not mandatory. Second, its occurrence in the elderly has led many doctors to adopt a conservative approach and to avoid surgery when possible. Most reported studies are based on histopathology and are thus an underestimation of the true incidence of this tumour. However, the authors' department is a national referral centre with a stable determinable catchment population. Furthermore, there has been no major change in the pattern of referrals noted, so that any increase in parotid tumour cases treated probably reflects an increase in incidence. The unit also consistently undertakes formal parotidectomies for all parotid masses for histological confirmation.

There is undeniably a strong association between smoking and the development of Warthin's tumour[4,5,7,10,15,16]. This is consistent even after stratifying for age and sex. Asians in general have a 40 times increased risk of developing Warthin's tumour if they smoke, compared with non-smokers. This aetiological factor could perhaps explain some of the differences in the epidemiology of Warthin's tumour noted in this population.

Contrary to most reported series in the West, Warthin's tumour in this series constituted a high proportion of all parotid tumours (25 per cent). The multicentricity in 19 per cent of patients with Warthin's tumour was also high. The rate of bilateral tumours of 10 per cent was consistent with that previously reported. The ratio of Warthin's tumour to pleomorphic adenomas in this series was 1 : 1·9. This supports the observation that there has been an increased incidence of Warthin's tumours relative to pleomorphic adenomas. Over the second half of the century, the occurrence of Warthin's tumour in the parotid gland has been reported to have increased from 6–10 per cent[17–19] to as high as 30 per cent[6,9]. This is probably due at least in part to the increase in smoking. Other factors include the more aggressive treatment of parotid masses with surgery[20] and the availability and reliability of cytological techniques of diagnosis[21].

Expressed as a proportion of all parotid neoplasms, Warthin's tumour did not show any increasing trend within the decade of study, in contrast to Western series (*Fig. 2*). In fact it has remained stable as smoking in Singapore has declined since the inception of the National Smoking Control Programme in 1986. Singapore's smoking prevalence rate dropped from 20 per cent in 1984 to 17 per cent in 1995[14] and this is below the 28 per cent rate in the USA in 1985[22]. The positive effects of this decline can also be sought in smoking-related cancers. Trends in lung cancer have been observed to parallel changes in tobacco consumption. Locally, most sex-ethnic groups showed an increase in lung cancer rates between 1968 and 1982, followed by a slight decrease until 1992[23].

The sex distribution of Warthin's tumours in this study continues to show a strong male predominance with a ratio of 4·6 : 1. This figure, although high, is lower than the earlier ratios of 10 : 1 – 7 : 1[17,19,24]. Most, if not all, studies of the past decade have reported decreasing male predominance to equal sex ratio[4,6,9]. There was no rising incidence of Warthin's tumours among women in this series probably because smoking in women is a relatively recent phenomenon and their consumption is low. The smoking prevalence rate (1995) is 32 per cent in men as opposed to 3 per cent in women[14]. The sex distribution of pleomorphic adenomas in this series shows the expected female predominance.

The paucity of Warthin's tumour in blacks (and possibly in other non-white populations) is noteworthy and interesting[3,5,7,18]. The racial distribution of Warthin's tumours appears to show an increased incidence among Chinese and a reduced incidence among Malays and Indians. This is despite a higher smoking prevalence rate in Malays and Indians compared with Chinese. This difference is difficult to explain by variation in lifestyle or other environmental influence, and suggests that genetic factors may be important.

The epidemiology of Warthin's tumour in the Asian population showed differences and similarities to that of Western series. This is partly explained by the differences in smoking rates between the communities. Smoking is an important and significant aetiological factor in tumour development although genetic factors, which need further evaluation, may also play a role.

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Case-controlled study of the epidemiological risk factors for breast cancer in Nigeria

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Background: The incidence of breast cancer is increasing worldwide, more rapidly in societies that hitherto enjoyed a low incidence of the disease, such as most African countries. Most of the epidemiological data on breast cancer from Africa have been retrospective studies with propensity for bias.
Methods: This was a case-controlled study of 250 consecutive patients with breast cancer diagnosed between April 1992 and December 1995. An age- and sex-matched control group of patients with non-oncological and non-endocrine diseases was compared.
Results: The peak age incidence of breast cancer in the sample studied was 43 years. There was a statistically significant difference in the height and weight of the patients compared with the controls. Patients also tended to be older at first pregnancy and at first lactation, and had a higher mean number of pregnancies. The patients also tended to be of an early birth order, to have lactated less often, to have used contraceptives and to have abused alcohol compared with the controls.
Conclusion: The incidence of breast cancer in this environment is increasing. This is partly a result of the changing demographic profile, acquisition of 'western' lifestyle, and the changing socioeconomic profile of the country.

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Introduction

Breast cancer is becoming more common worldwide. In North America, the lifetime risk of breast cancer is 10·0 per cent for white and 7·3 per cent for black women. Some 3 5 per cent will die from breast cancer[1]. The incidence of breast cancer is rising more rapidly in population groups that hitherto enjoyed a low incidence of the disease. The incidence in Nigeria in 1976 was 15·3 per 100 000[2] but this had risen to 33·6 per 100 000 by 1992[3]. Despite this doubling in incidence, many clinicians believe that there is under-reporting owing to low awareness, poor access to medical services, poverty, sociocultural factors and absence of a breast screening programme[4].

Between 1960 and 1980, the cancer registry of this hospital recorded 17 496 cases of cancer. Breast cancer was the fourth commonest tumour overall (6·0 per cent) and the second commonest in women. However, between 1980 and 1989 it had become the commonest malignancy seen. This trend has been confirmed in studies from other parts of Africa[5–9].

The variable incidence of breast cancer in different parts of the world suggests that environmental influences are important in the aetiology. Identification of these factors may enhance the ability to prevent the disease by permitting better focused health education and other preventive strategies.

The present report is a case-controlled study of 250 consecutive patients with breast cancer.

Patients and methods

All consecutive patients (from a single tribe) who presented to the Oncology Clinic of this hospital between April 1992 and December 1995 were recruited. Diagnosis of breast cancer was made by either excision, incision, core-needle or fine-needle aspiration biopsy. Patients were individually matched by age (within a 1-year age band) and sex with 250 inpatients admitted to the general surgical service during the same interval but with non-endocrine, non-malignant diseases. The admission diagnosis in controls included abdominal and soft tissue trauma, gallbladder disease, haemorrhoids, fistula *in ano*, anal fissure, peptic ulcer disease and its complications, and complications of typhoid enteritis.

Using a protocol administered by a trained nurse, the following information was obtained from patients and controls: weight, height, age at menarche, menstrual cycle history, age at first pregnancy, parity, number of miscarriages, age at first lactation, history of previous breast disease, smoking, and history of drug and alcohol abuse. Other information obtained included birth order, first-degree family history and history of use of oestrogen-containing contraceptives

Numerical data were expressed as mean(s.d.) and the *t* test was used to compare patients and controls. Odds ratios were calculated for proportions and exact confidence limits were obtained. χ^2 with Yates' correction was used to test the difference between proportions.

Results

The majority of the 250 patients presented with advanced breast cancer. There were no T_1 tumours. Some 72·8 per cent had Manchester Stage III or IV breast cancer; axillary nodes were involved at diagnosis in 95·6 per cent. A total of 12·0 per cent were pregnant or lactating and 74·0 per cent were premenopausal. Patients with breast cancer were taller and heavier than control subjects (*Table 1*). The mean age at menarche was similar in both groups. Six per cent of controls could not recall their age at onset of menstruation compared with 12·0 per cent of those with breast cancer. There was a statistically significant difference in the age at first full-term pregnancy and in the age at first lactation between the groups. Contrary to the expectation that multiparity protects against breast cancer, control patients had a mean of 4(1) (range 2–9) pregnancies compared with 6(2) (range 0–12) in patients with breast cancer ($P < 0·0001$).

Patients with breast cancer tended to be of an early birth order compared with controls; more were first or second born children (*Table 2*). While all control patients breastfed, 13·2 per cent of those with breast cancer did not (including the 1·6 per cent who were nulliparous). None of the controls was nulliparous. A positive family history was obtained in five patients with breast cancer (2·0 per cent) compared with only one (0·4 per cent) in the control group. All members of the control group who reported a history of breast disease (3·2 per cent) had a lactational breast abscess. Of the 12·0 per cent of patients with breast cancer who reported previous benign breast disease, all but one had a lactational breast abscess. The histological diagnosis in the remaining patient was not known.

Table 1 Comparison between patients with breast cancer and controls

	Patients (*n* = 250)	Controls (*n* = 250)	*t*	*P*
Age (years)	43(8)	43(9)	0·14	0·61
Weight (kg)	66(8)	64(13)	2·62	0·01
Height (cm)	158(7)	147(8)	16·28	<0·0001
Age at menarche (years)	15(2)	16(3)	0·80	0·423
Age at first full-term pregnancy (years)	22(3)	20(2)	10·79	<0·0001
No. of pregnancies	6(2)	4(1)	14·10	<0·0001
Age at first lactation (years)	23(3)	21(2)	16·49	<0·0001

Values are mean(s.d.)

Table 2 Comparison of proportions between patients with breast cancer and controls

	Patients (*n* = 250)	Controls (*n* = 250)	Odds ratio	χ^2‡	*P*
Birth order*	175	117	2·65 (1·81–3·90)	26·75	<0·0001
Menstrual irregularity†	8	7	1·15 (0·36–3·78)	0·00	1·000
Miscarriage	110	103	1·12 (0·77–1·62)	0·29	0·587
Lactation	217	250	0·00 (0·00–0·10)	33·22	<0·0001
Contraceptive use	10	2	5·17 (1·08–48·85)	4·18	0·041
Family history	5	1	5·08 (0·56–241·29)	1·52	0·218
Alcohol	8	0	—	6·22	0·012
Nulliparity	4	0	—	2·27	0·132

Values in parentheses are exact 95 per cent confidence intervals

*First or second born, † abnormal cyclical bleeding pattern. ‡With Yates' correction

Some 3·2 per cent of patients with breast cancer volunteered a history of regular alcohol use: the mean volume consumed per month was 300 ml of 5·0 per cent w/v. None of the controls regularly used alcohol. There was no reported use of tobacco in either group of patients.

Some 4·0 per cent of patients with breast cancer had used oral contraceptives compared with 0·8 per cent of the controls. All respondents claimed that they used contraception intermittently and none could remember the name of the agent.

Discussion

It is estimated that 984 000 new cases of breast cancer will develop worldwide in the year 2000[10]. While some of the increase is due to demographic change[11], there is also a real increase in incidence, which is greatest in some developing countries that hitherto enjoyed a low incidence. Data from the latter are scanty and tend to be retrospective case series[5–9].

In this prospective case-controlled study of the epidemiological risk factors of breast cancer in Nigerian women, the mean patient age of 43 years is similar to previous observations from other centres in Africa[3–9,12,13].

This relatively low peak age incidence can probably be explained by the low life expectancy at birth of women in this environment (52 years for Nigerian women in 1992; Federal Ministry of Health of Nigeria statistics) and the age and sex pattern of the population. In Nigeria, women aged 15–44 years constituted 22·8 per cent of the population in 1991. Age-standardized incidence ratios are needed to unravel the true age incidence of the disease in this population. Since the incidence of breast cancer rises with age in Caucasian series, it is possible that as the life expectancy of African populations increases the incidence of breast cancer will rise.

Several studies have highlighted the role of prolonged exposure to endogenous oestrogen hormone as a risk factor for breast cancer[14–17]. Early onset of menarche, late onset of menopause, low parity, older age at first full-term pregnancy and lactation are associated with a greater risk of developing breast cancer. In this study, the mean age of onset of menstruation in both study and control groups was about 15 years. While there was a statistically significant difference in the age at first full-term pregnancy, at first lactation and in the mean number of pregnancies between the controls and patients, these risk factors were still infrequent in the study population. Age at menarche decreases while that at menopause increases as a society gets more affluent and living standard improves[11]. Likewise the demands of education and a career may increase the number of women who delay childbearing. With better health care facilities and increased contraceptive use, women will also have fewer pregnancies. The prolonged endogenous exposure to hormones that results from these changes may contribute to a higher incidence of breast cancer in the future.

Maternal birth order appeared to be a strong risk factor for the development of breast cancer in this study. Ekbom and others[18–20] have suggested that maternal oestrogen levels are high during early pregnancy and that this may influence the later development of breast cancer. This factor may contribute to a higher incidence of breast cancer in future as women have fewer children, more of whom survive into adulthood. Hence a greater ratio of these children will be early-order births.

Contraception is rarely used in Nigeria (10 per cent in 1994; Federal Ministry of Health of Nigeria statistics) but there have been recent efforts to change this as part of measures to control population growth. While the relationship between contraceptive use and breast cancer remains a matter for debate, the present study showed a statistically significant difference between patients with breast cancer and controls[3,21].

The paucity of data on previous breast biopsy and histology is due to low utilization of health care facilities and low awareness of breast disease in the population. All but one of the respondents who reported previous benign breast disease had a breast abscess. The latter is painful, unlike other benign breast diseases that tend to present as a painless breast lump. Patients are therefore likely to seek help.

Family history of breast cancer is difficult to elicit in this environment for several reasons. Cancer diagnosis is seldom discussed, even with family members. Lack of records, social taboos[22], fear of stigmatization and a low life expectancy all contribute to the lack of data.

The results of this study must be interpreted in the light of possible biases that case-controlled studies like this are subject to. The power of the study would have been improved by a larger sample size but this was not possible owing to limitation of funds. A population sample (rather than hospital-based patients) used as a control group would have increased the validity of the conclusions drawn. Case-controlled studies are prone to recall bias, as the patients tend to be more inquisitorial about any possible risk factor than the controls.

The findings in this study suggest that the incidence of breast cancer in Nigeria may rise in future, largely as a result of factors that cannot be prevented. There is a need to prepare for this by increasing public awareness and investing in the human and material resources for treatment. Studies of 'low-tech', low-cost management options as well as scrutiny of the role of genetic risk factors in the identification of an at-risk population are urgently required.

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Original article

Unique distribution patterns of metastatic lymph nodes in patients with superficial carcinoma of the thoracic oesophagus

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Background: Lymph node metastasis is commonly found in carcinoma of the thoracic oesophagus, even when the tumour invades only the submucosa. Although lymph node status greatly influences the outcome, the pattern of early lymphatic spread has not been investigated, and the role of lymph node dissection is still a matter of controversy.

Methods: A series of 110 patients with superficial carcinoma who underwent systematic extended lymph node dissection was investigated retrospectively.

Results: Lymph node involvement was found in 0 per cent (none of nine), 23 per cent (five of 22) and 49 per cent (38 of 78) of tumours that invaded the lamina propria, muscularis mucosa and submucosa respectively. Anatomically distant lymph nodes (recurrent nerve nodes and perigastric nodes) were involved more frequently than other intrathoracic nodes adjacent to the main tumour. Only three patients had involvement limited to the intrathoracic group, and in carcinoma that invaded only the muscularis mucosae, all metastatic nodes were located at the thoracocervical junction or in the abdomen. The 5-year survival rate was 89 per cent in the node-negative group and 54 per cent in the node-positive group ($P < 0.0003$).

Conclusion: The recurrent nerve nodes and perigastric nodes are the principal proximal regional lymph nodes involved in superficial carcinoma of the thoracic oesophagus. Systematic lymph node dissection, which included these nodes, yielded an acceptable and favourable outcome in patients with node-positive superficial carcinoma.

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Introduction

Patients with mucosal and submucosal carcinoma (superficial carcinoma) of the thoracic oesophagus have recently increased in number owing to progress in oesophagoscopic surveillance[1–4]. Although superficial oesophageal carcinoma is categorized in the Union Internacional Contra la Cancrum pathological tumour node metastasis (pTMN) classification[5] as pT_{is} or pT_1, lymph node involvement is commonly found in patients with superficial carcinoma, and it greatly influences outcome after oesophagectomy[1,3,4,6]. Several authors have reported that involved lymph nodes are distributed over a wide anatomical range from the neck to the upper abdomen[3,6]. However, the relationship between the degree of superficial wall invasion and the pattern of lymphatic spread has not yet been well investigated, and the role and reasonable extent of lymph node dissection for superficial carcinoma is still a matter of controversy[7,8].

In the present study, the pattern of lymph node metastasis was analysed and its influence on outcome in patients with superficial squamous cell carcinoma treated at a single institution by a unique extensive lymph node dissection procedure was determined. The study also provided information on the oesophageal lymphatic drainage system, which should be useful for the treatment of more advanced oesophageal carcinoma.

Patients and methods

Of 522 patients who underwent oesophagectomy for squamous cell carcinoma of the thoracic oesophagus between 1985 and 1997, 166 had a primary tumour which invaded only the mucosal or submucosal layer. The anatomical distribution of the involved lymph nodes was investigated retrospectively in 110 patients with superficial carcinoma who underwent systematic dissection of cervical, mediastinal and abdominal regional lymph nodes, excluding patients with previous or synchronous squamous cell carcinoma of the head and neck region and those who underwent oesophagectomy without thoracotomy or with limited nodal dissection. No patient had received preoperative therapy. The main tumour was located in the upper third of the thoracic oesophagus in 13 patients, in the middle third in 73 and in the lower third in 24.

The regional lymph nodes dissected during the routine procedure were classified into four groups: the deep cervical node group, recurrent nerve node group, intrathoracic node group and perigastric node group (*Fig. 1*). The recurrent nerve node group includes lymph nodes located immediately adjacent to the bilateral recurrent nerves at the thoracocervical junction. Although the lower portion of these nodes is located in the thorax, all recurrent nerve nodes were regarded as a single group and distinguished from the other intrathoracic lymph nodes because they have special clinical significance. The perigastric group included the lymph nodes beside the cardia of the stomach and nodes around the left gastric artery and coeliac artery. Lymph node dissection was performed through a collar-shaped cervical incision, laparotomy and thoracotomy. When a narrow operation field was anticipated during the cervical procedure, median sternotomy or partial resection of the manubrium was performed to obtain a wider view of the thoracocervical junction[9]. Thoracotomy was performed principally on the right side. Left thoracotomy was selected in 12 patients: seven at poor risk for right thoracotomy and five with carcinoma confined to the lowest part of the oesophagus.

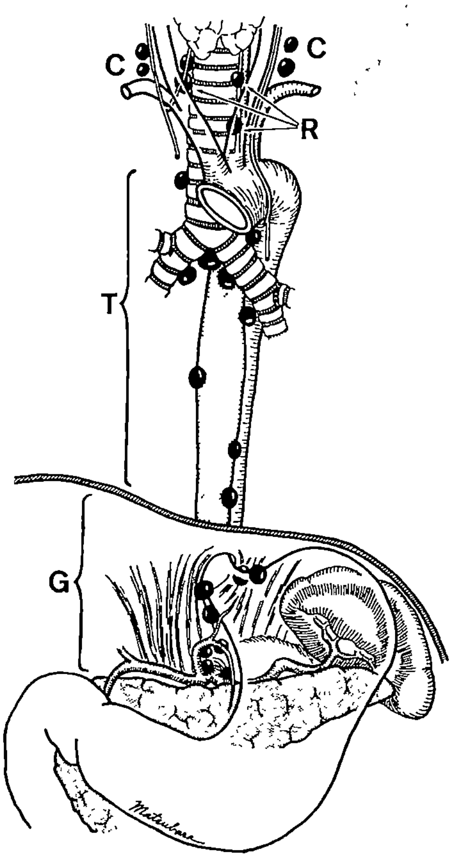


Fig. 1 Regional lymph nodes dissected during routine procedure: C, deep cervical lymph nodes; R, recurrent nerve lymph nodes; T, intrathoracic lymph nodes; G, perigastric lymph nodes

The superficial layer of the oesophagus is divided into the epithelium (ep), lamina propria (lp), muscularis mucosae (mm) and submucosa. Submucosal carcinoma invasion was classified histopathologically in three categories: invasion slightly beyond the muscularis mucosae (sm1), invasion close to the muscularis propria (sm3) and intermediate submucosal invasion (sm2). The entire resected oesophagus was divided into transverse sections 7 mm or less in width, and all sections were examined histopathologically.

Survival curves were constructed according to the Kaplan–Meier method, and differences in survival outcomes were evaluated with the generalized Wilcoxon method.

Results

Lymph node involvement was found in 43 (39 per cent) of the 110 patients with superficial carcinoma. The recurrent nerve node group was involved most frequently, followed by the perigastric node group. A majority of patients with involvement of the recurrent nerve node group or perigastric node group did not show involvement of other node groups (*Table 1*). Recurrent node involvement was found on the right side in 12 patients, the left side in seven and was bilateral in five. Of the 18 patients with perigastric node involvement, eight had coeliac node involvement. The frequency of nodal involvement increased with deeper invasion. However, even in the mm-carcinoma cases, five of the 22 patients had positive nodes; none of them had involvement of the intrathoracic node group (*Table 2*). When the proximal tumour margin was in the

Table 1 Metastasis to regional lymph node groups in 110 patients with superficial carcinoma of the oesophagus

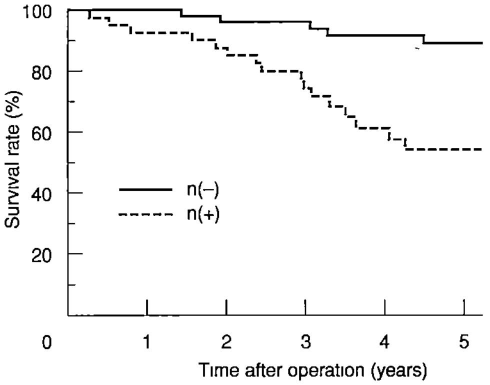
Nodal group	No. of patients	Exclusive involvement*
Deep cervical	4	1
Recurrent nerve	24	17
Intrathoracic	9	3
Perigastric	18	12

*Involvement limited to a single nodal group

Table 2 Depth of tumour invasion and metastasis to regional lymph nodes

	Depth of tumour invasion					
Nodal site	ep ($n = 1$)	lp ($n = 9$)	mm ($n = 22$)	sm1 ($n = 12$)	sm2 ($n = 39$)	sm3 ($n = 27$)
Deep cervical	0	0	1	0	1	2
Recurrent nerve	0	0	3	1	10	10
Intrathoracic	0	0	0	1	5	3
Perigastric	0	0	1	1	7	9
Node positive	0	0	5	3	17	18

ep, epithelium, lp, lamina propria; mm, muscularis mucosae; sm, submucosa



No at risk						
n(–)	67	59	48	44	39	34
n(+)	43	38	34	26	18	15

Fig. 2 Kaplan–Meier survival curves after oesophagectomy in patients with superficial carcinoma: n(–), no nodal involvement, n(+), nodal involvement. $P < 0.0003$ (Wilcoxon test)

middle third of the oesophagus, 13 (19 per cent) of 67 patients had recurrent nerve node involvement. Perigastric node involvement was observed in six (12 per cent) of 50 cases in which the distal tumour margin was in the middle third of the oesophagus, but was not found in nine patients in whom the main tumour did not invade the lower two-thirds of the oesophagus.

Postoperative complications occurred in 43 patients (39 per cent). Common complications included recurrent laryngeal nerve palsy (left palsy in 11 patients, right palsy in three and bilateral in four), leakage or necrosis of the oesophageal substitute (major leakage in seven, minor leakage in five) and pulmonary complications (six patients). Tracheotomy was performed in eight patients. Hoarseness due to recurrent nerve palsy resolved within 6 months after oesophagectomy in all but one patient.

One patient died during the hospital stay, the hospital mortality rate being 1 per cent. The overall 5-year survival rate was 75 per cent. Outcome was significantly correlated with lymph node status: the 5-year survival rate in the node-negative group was 89 per cent, compared with 54 per cent in the node-positive group (*Fig. 2*). It was noteworthy that the 5-year survival rate in the 29 patients in whom nodal involvement was limited to the recurrent nerve nodes or perigastric nodes was 62 per cent. Of the 15 patients who survived more than 5 years in the node-positive group, 14 had involvement of the recurrent nerve nodes or perigastric nodes, and three had coeliac node involvement. Cancer recurrence was confirmed clinically in 15 patients (*Table 3*). Of the five patients who died within 5 years in the node-negative group, only two died from recurrence of carcinoma.

Table 3 Recurrence of carcinoma following oesophagectomy with systematic lymph node dissection in superficial carcinoma of the thoracic oesophagus

	Nodal status at oesophagectomy	
Site of recurrence	n(–)	n(+)
Locoregional		
Neck or mediastinum	1	2
Abdominal periaortic	1	3
Haematogenous		
Lung	2	2
Liver	0	3
Mixed	0	1*

n(–), Patients without nodal involvement, n(+), those with nodal involvement *Liver and abdominal periaortic recurrence

Discussion

Lymph node status is a major prognostic factor in superficial carcinoma of the oesophagus[1,3,4]. In node-negative patients, the survival rate after oesophagectomy was significantly more favourable and carcinoma recurrence due to haematogenous metastasis was rare. These findings strongly suggest that extraoesophageal invasion from superficial oesophageal carcinoma first develops through lymphatic pathways more frequently than via the haematogenous route. Thus, carcinoma spread may still be confined to the oesophagus and regional lymph node groups in a considerable proportion of patients with superficial carcinoma. However, the role of lymph node dissection for superficial oesophageal carcinoma is not yet generally recognized. Most Western surgeons regard nodal involvement in oesophageal carcinoma as a sign of systemically disseminated disease, because patients with nodal involvement in their series have shown unfavourable outcomes[1,8,10,11].

When previous reports were analysed according to the extent of lymph node dissection, major differences in the frequency of lymph node metastasis from pT_1 carcinoma were found. Authors who performed extensive lymph node dissection[3,6,7] reported metastatic rates twice as high as those who performed less extensive dissection[1,4]. This suggested that pT_1 carcinoma frequently metastasizes to lymph nodes that are not totally dissected during less extensive operations. The present study demonstrated that the recurrent nerve node group and perigastric node group, including the coeliac nodes, were involved more frequently than other mediastinal nodes adjacent to the main tumour. Moreover, metastasis limited to either the recurrent nerve node group or the perigastric node group was found to be common. Special attention should be paid to the finding that the intrathoracic lymph nodes adjacent to the main tumour were all negative in five node-positive cases with carcinoma that had invaded only the muscularis mucosae. Presumably the presence of abundant lymphatic channels in the mucosa and submucosa of the oesophagus[12] allows oesophageal carcinoma to metastasize to anatomically distant lymph nodes[13]. Since these superficial lymphatic channels run in the longitudinal direction of the oesophagus, metastasis to the recurrent nerve nodes and perigastric nodes frequently occurs earlier than intrathoracic metastasis in superficial carcinoma. Therefore, patients with extrathoracic nodal involvement may have no further metastatic lesions beyond these lymph nodes. Actually, 62 per cent of the patients in whom metastatic nodes were found only in the recurrent nerve node group or perigastric node group were alive 5 years after operation, and all of the 15 5-year survivors with positive nodes had involvement of the recurrent nerve nodes or perigastric nodes, except one patient. These results strongly suggest that recurrent nerve nodes and perigastric nodes should be regarded as the proximal regional lymph nodes of the intrathoracic oesophagus.

Extensive lymph node dissection increases the risk of operative complications, such as cardiopulmonary dysfunction and recurrent nerve palsy. The present study suggested that less aggressive dissection procedures are applicable for poor-risk patients with superficial carcinoma. Since the intrathoracic node group is involved less frequently than lymph nodes that can be dissected through cervical incision and laparotomy, the second best operation for superficial carcinoma may be oesophagectomy without thoracotomy with cervical and abdominal dissection. For carcinoma confined to the upper third of the oesophagus, abdominal dissection may be avoided.

In conclusion, the frequency of lymph node involvement was high in patients with carcinoma invading the muscularis mucosae or submucosa of the oesophagus. Cancer commonly metastasized to recurrent nerve lymph nodes and perigastric lymph nodes across a considerable anatomical distance. These nodes were involved more frequently than adjacent intrathoracic lymph nodes. Extensive lymph node dissection, including these nodes, yielded an acceptable, favourable outcome in node-positive patients.

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Clinical significance of telomerase activity in the non-cancerous epithelial region of oesophageal squamous cell carcinoma

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Background: The aim of this study was to examine telomerase activity in affected and adjacent tissue in patients with oesophageal squamous cell carcinoma (SCC).
Methods: Telomerase activity was measured in oesophageal SCC cells, normal oesophageal culture cells, primary cancer tissues and adjacent normal tissues from patients with oesophageal SCC using a polymerase chain reaction-based assay.
Results: All oesophageal SCC cells had telomerase activity, whereas normal cultured cells showed no activity. All 57 cancer tissues showed telomerase activity compared with only five (10 per cent) of 50 normal tissues. Cancer cells infiltrating the vessels of mucosal or submucosal tissues in non-cancerous regions were detected in four of five telomerase-positive normal tissues, whereas such infiltration was detected in only three of 45 telomerase-negative normal tissues.
Conclusion: In patients with oesophageal SCC, measurement of telomerase activity in normal epithelium is a highly sensitive method of detecting the microinvasion of cancer cells.

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Introduction

Oesophageal squamous cell carcinoma (SCC) is one of the most aggressive cancers and is associated with a poor survival rate. The cancer is usually invasive by the time diagnosis is made. Cellular progression to malignancy is thought to involve multistep events, and is expressed histologically as a progression from normal epithelium to cancerous tissue[1,2]. Recent studies have demonstrated genetic alterations in oesophageal SCC, especially mutational activation or overexpression of oncogenes and loss of the normal function of tumour suppressor genes[3–5]. In addition to such genetic alterations, cellular immortalization is required for malignancy.

Telomeres are specialized structures at the ends of eukaryotic chromosomes that consist of tandem repeats of the TTAGGG and associated proteins[6]. Cellular DNA polymerases cannot replicate the 5′ end of the linear DNA molecule (referred to as the end-replication problem)[7–10]. The continuous shortening of telomeres may be the mitotic clock by which cells count their divisions[11]. Sufficiently shortened telomeres may be the signal for replicative senescence in normal cells[9,10]. Immortalized cancer cells can escape from replicative senescence and proliferate indefinitely[12–14].

Telomerase is a ribonucleoprotein enzyme that adds telomeric sequences (TTAGGG) on to chromosomal ends by means of an internal RNA template complementary to the TTAGGG repeats[15,16]. Evidence has been accumulating that telomerase activity is present in almost all immortal cancer cells and germline cells, whereas no activity is detectable in mortal culture cells[17]. Expression of telomerase activity has also been found in many primary tumour tissues, but not in most tissues adjacent to the primary tumour, nor in virtually any other normal tissues, except for germline cells and peripheral blood leucocytes[18–24].

In some of the genetic analyses a small number of cancer cells was considered to have spread already into several lymph nodes in which no cancer cells were detectable by histopathological examination. Genetically diagnosed lymph node metastasis may thus be a useful prognostic factor[25–27]. Measurement of telomerase activity is thought to be highly sensitive; therefore, positive telomerase activity in histopathologically normal tissues may indicate occult invasion.

In this study telomerase activity was measured in immortal cancer cells obtained from oesophageal SCC and in normal culture cells derived from the oesophageal wall. In addition, the telomerase activity of primary tumour tissues and adjacent normal tissues obtained from surgically resected specimens was determined and related to prognosis.

Patients and methods

Culture cells

Fourteen ESCC cell lines (TE1–6 and TE8–15) were provided by Dr T. Nishihira (Tohoku University, Sendai, Japan). Normal oesophageal culture cells (epithelial cells, fibroblasts, smooth muscle cells) derived from the oesophageal wall were cultured carefully in this laboratory. These normal cells underwent cellular senescence after several divisions in culture. All cells were grown in Dulbecco's modified Eagle's medium supplemented with 10 per cent fetal calf serum and maintained in a humidified atmosphere of air containing 5 per cent carbon dioxide at 37°C.

Clinical samples

Resected specimens were obtained from 57 patients who underwent oesophagectomy for previously untreated oesophageal SCC at Keio University Hospital between 1994 and 1996, and provided a total of 57 primary tumour tissues and 50 corresponding normal tissues. Normal epithelium as determined by iodine staining was sampled at a distance of 5 cm from the oesophageal tumour. Glycogen produced in normal squamous epithelium reacts with iodine, staining the normal epithelium brown, whereas squamous cell carcinoma tissues, which have less glycogen, are not stained by iodine. The specimens of normal tissue included both mucosal and a part of the submucosal layer. The samples were snap-frozen in liquid nitrogen and stored at –80°C. Histopathological examination was performed under the guidelines established by the Japanese Society for Oesophageal Diseases and the stage grouping was classified according to the pathological tumour node metastasis (pTNM) classification for the oesophagus[28,29].

Telomerase assay

Samples were suspended in ice-cold wash buffer (Hepes–potassium hydroxide 10 mmol/l (pH 7·5), magnesium chloride 1·5 mmol/l, potassium chloride 10 mmol/l, dithiothreitol 1 mmol/l), pelleted at 10 000*g* for 5 min at 4°C, and then repelleted, homogenized and resuspended in 200 µl ice-cold lysis buffer (Tris–hydrochloric acid 10 mmol/l (pH 7·5), magnesium chloride 1 mmol/l, EGTA (ethylene glycol bis (*β*-aminoethyl ether)-N,N,N′,N′,-tetra-acetic acid) 1 mmol/l, 4-(2-aminoethyl)benzenesulphonylfluoride hydrochloride (AEBSF) 0·1 mmol/l (Sigma, St Louis, Missouri, USA), *β*-mercaptoethanol 5 mmol/l, 0·5 per cent 3-((3-cholamidopropyl) dimethylammonio)-1-propanesulphonate (CHAPS) (Sigma), 10 per cent glycerol). The suspension was incubated for 30 min at 4°C, the lysate was centrifuged at 16 000*g* for 20 min at 4°C, and the supernatant was removed, rapidly frozen on dry ice and stored at –80°C. Protein concentrations were measured using a Micro Bicinchoninic Acid Protein Assay Reagent Kit (Pierce Chemical, Rockford, Illinois, USA), and extracts were adjusted to 6, 0·6 and 0·06 µg of the standard protein for each assay. For ribonuclease (RNAase) treatment, 5-µl extracts were incubated with 1 µg RNAase A for 20 min at 37°C.

The telomeric repeat amplification protocol (TRAP) assay was performed as follows[17]. Serially diluted extracts were assayed in 50 µl TRAP reaction solution containing Tris–hydrochloric acid 20 mmol/l (pH 8·3), magnesium chloride 1·5 mmol/l, potassium chloride 63 mmol/l, 0·005 per cent Tween 20, EGTA 1 mmol/l, 50 µmol/l of each deoxynucleotide triphosphate, 0·1 µg deoxyoligonucleotide TS primer (5′-AATCCGTCGAGCAGAGTT-3′), 1 µg T4 gene 32 protein (Boehringer Mannheim, Mannheim, Germany), bovine serum albumin 0·1 mg/ml, 2 units AmpliTaq DNA polymerase (Perkin Elmer, Branchburg, New Jersey, USA), 0·4 µl [α-^{32}P]deoxycytidine triphosphate and [α-^{32}P]thymidine triphosphate, in a 0·5-ml tube containing 0·1 µg deoxyoligonucleotide CX primer (5′-CCCTTACCCTTACCCTTACCCTTA-3′) at the bottom and sealed with 7 µl molten wax (Ampliwax PCR Gem 100; Perkin Elmer). After 30 min of incubation at 23°C to allow telomerase-mediated extension of the TS primer, the reaction mixtures were heated at 90°C for 90 s to inactivate the telomerase. Assay tubes were then transferred to 31 polymerase chain reaction (PCR) cycles at 94°C for 30 s, 50°C for 30 s, and 72°C for 50 s. The CX primer was liberated when the wax barrier melted at 70°C. The PCR products were analysed by electrophoresis in 0·5 × Tris–borate ethylenediamine tetra-acetic acid (Tris 45 mmol/l, Boric acid 45 mmol/l, EDTA 1·25 mmol/l) on 10 per cent polyacrylamide non-denaturing gels at 200 V for 2 h. The gels were scanned using a Bioimage Analyser (BAS 2000; Fuji, Tokyo, Japan). The extracts that produced 6-base pair DNA ladders extending from 40 base pairs, and were also sensitive to RNAase A, were considered to be telomerase positive.

Statistical analysis

Patient groups were compared with the χ^2 test. Disease-free survival rates for patient groups were calculated by means of the Kaplan–Meier method and compared with the log rank test. $P < 0\cdot05$ was considered statistically significant.

Results

Culture cells

Telomerase activity was detected in all oesophageal SCC cell line extracts (TE1–6 and TE8–15), even at a dilution of 0·06 μg protein, and disappeared with RNAase A pretreatment. In contrast, normal oesophageal culture cells showed no telomerase activity (*Fig. 1a*).

Clinical samples

All 57 oesophageal SCC tissues had detectable telomerase activity (*Fig. 1b*). However, telomerase activity was detected in only five (10 per cent) of the 50 adjacent normal oesophageal epithelial regions. Telomerase activity was detected even with 0·06 μg protein in 21 cancer tissues (37 per cent) (strong effect). In 11 cancer tissues (19 per cent) telomerase activity was detected only with 6 μg protein (weak effect), and in the 25 other cancer tissues (44 per cent) telomerase activity was detected with 6 and 0·6 μg of protein (moderate effect). There were no differences in histopathological findings among these three groups (data not shown). The normal epithelial regions were divided into two groups (a telomerase-positive normal tissue group and a telomerase-negative normal tissue group) and the histopathological findings of adjacent tumour tissues were compared (*Table 1*). There was a significant difference in blood vessel invasion at the tumour lesion between the patients with telomerase-positive normal tissues and those with no telomerase activity. Patients with positive telomerase activity in normal tissues clearly had a higher incidence of both lymphatic invasion and lymph node metastasis, although the increases were not statistically significant. There was no significant difference in postoperative adjuvant therapy between the patients with telomerase-positive normal tissues and those with no telomerase activity (data not shown).

Detailed histopathological examination of all specimens also revealed cancer cells to have infiltrated blood or lymphatic vessels of the mucosal or submucosal layer in adjacent normal epithelial regions in four of the five telomerase-positive normal tissues (*Fig. 2*), whereas such findings were detected in only three of the 45 telomerase-negative normal tissues. All five telomerase-positive cases and 35 of the 45 with telomerase-negative normal tissues showed blood or lymphatic vessel invasion of the adjacent tumour. Patients in the telomerase-positive normal tissue group had a poor outcome: four of five patients died within 11 months of surgery, and in the remaining patient lymph node metastasis was detected 23 months after operation.

Disease-free survival rates were compared between patients with telomerase-positive and telomerase-negative normal tissue. The rate was significantly higher for the 45 patients with telomerase-negative normal tissue: 35 (78 per cent) were alive at 4 years ($P < 0\cdot001$) (*Fig. 3*).

Patients with and without telomerase activity in normal tissue were stratified according to histological stage. There were five patients with telomerase-positive normal tissue and 26 with telomerase-negative normal tissue in stage IIB and III group. The disease-free survival rate in the positive group was significantly lower than that in the negative

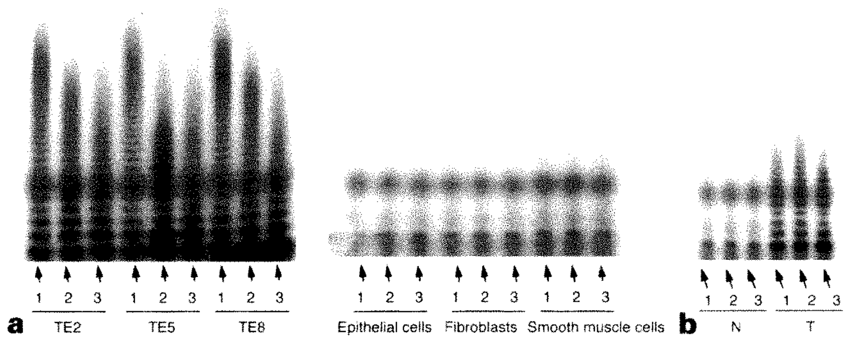

Fig. 1 Telomerase activity in oesophageal squamous cell carcinoma (SCC) cells, normal oesophageal culture cells (epithelial cells, fibroblasts, smooth muscle cells) and tissue samples. 1, 2, 3: Assays of extracts containing 6, 0·6 and 0·06 μg protein respectively. **a** Oesophageal SCC cell (TE2, TE5, TE8) extracts showed 6-base-pair ladder signals extending from 40 base pairs even with 0·06 μg protein, but the normal culture cell extracts showed no signals. **b** In adjacent normal oesophageal epithelial tissues (N), no telomerase activity was detected. The tumour tissue (T) extracts showed telomerase activity even with 0·06 μg protein

Table 1 Association between histopathological findings of adjacent tumour and telomerase activity in normal epithelium (5 cm from tumour) in surgically resected specimens

Histopathological findings of tumour lesion	Telomerase activity in normal lesion		P§
	Positive	Negative	
Primary tumour*			
pT_1	0	17	0·34
pT_2	1	6	
pT_3	3	19	
pT_4	1	3	
Regional lymph node†			
pN_0	0	19	0·06
pN_1	5	26	
TNM staging			
I	0	12	0·23
IIA	0	7	
IIB	1	10	
III	4	16	
Lymphatic invasion‡			
No	0	13	0·16
Yes	5	32	
Blood vessel invasion‡			
No	0	31	0·01
Yes	5	14	

TNM, tumour node metastasis. $^*pT_1$, tumour invades lamina propria or submucosa; pT_2, tumour invades muscularis propria; pT_3, tumour invades adventitia; pT_4, tumour invades other organs. $^\dagger pN_0$, no regional lymph node metastasis; pN_1, regional lymph node metastasis. ‡Each histopathological finding was judged according to the guidelines of the Japanese Society for Oesophageal Diseases[28]. §χ^2 test

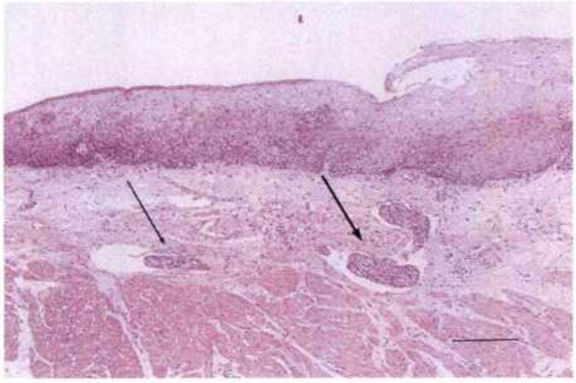

Fig. 2 Cancer cells are seen to infiltrate lymphatic vessels of the mucosal layer in a normal epithelial region in telomerase-positive normal tissue, 5 cm from the oesophageal squamous cell carcinoma. Scale bar is 200 μm

group, which was 18 (72 per cent) at 3 years ($P < 0·005$). Patients in both groups were stratified according to pT factors. The disease-free survival rate in the positive group was significantly lower than that in the negative group ($P < 0·05$; data not shown). Patients in both groups were then stratified according to pN factors. The disease-free survival rate in the positive group was significantly lower than that in the negative group ($P < 0·005$; data not shown). Patients with telomerase-positive and telomerase-negative normal tissues were then stratified according to vascular invasion at the tumour. All five patients with telomerase-positive normal tissue had both lymphatic invasion and blood vessel invasion, and 35 of the 45 patients with telomerase-negative normal tissue had lymphatic or blood vessel invasion. The disease-free survival rate in the positive group was significantly lower than that in the negative group: 26 (75 per cent) at 3 years ($P < 0·001$).

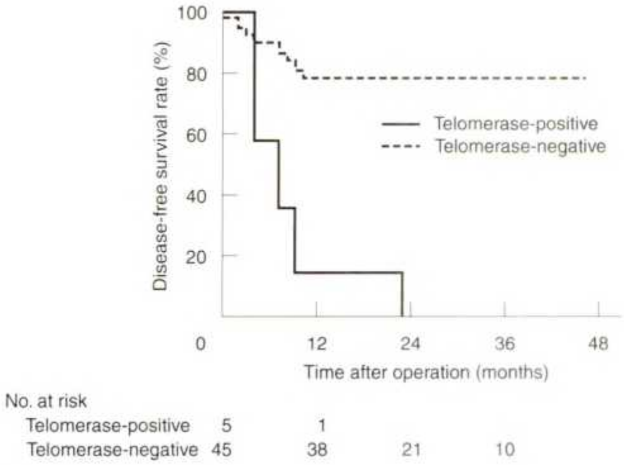

Fig. 3 Disease-free survival rates of patients with and without telomerase activity in adjacent normal epithelial regions obtained from surgically resected specimens. $P < 0·001$ (telomerase-positive *versus* telomerase-negative, log rank test)

Discussion

In this study, telomerase activity was detectable only in oesophageal SCC cells, not in other cultured cells derived from the oesophageal wall, and this activity was detected in 100 per cent of ESCC tissues. Telomerase activity was detected in five of the 50 normal epithelial regions and microinvasion of cancer cells through vessels in the mucosal or submucosal layer was thought to account for the positive activity in normal epithelium. The disease-free survival rate of patients with telomerase-positive normal tissues was significantly lower than that of those with telomerase-negative normal tissues.

These findings agree with those of others that telomerase activity is expressed only in immortalized cells, but not in other cultured cells from the oesophageal wall, and that telomerase reactivation is associated with overcoming the cellular senescence in normal oesophageal cells[17].

Transformed cells may undergo cellular senescence in an event called M2 crisis[30]. To escape the M2 crisis, transformed cells apparently require telomerase reactivation by an unknown mechanism[11]. Telomerase activity has previously been detected in 85–90 per cent of tumour tissues and was detected in 88 per cent of squamous cell lung carcinoma[19]. In this study, telomerase activity was detected in all oesophageal SCC tissues, suggesting these tissues contain immortalized cells that overcome the M2 crisis and also that telomerase reactivation is essential for carcinogenesis of normal oesophageal epithelium. These findings also suggest that oesophageal SCC cells already have undergone numerous cell divisions and have stabilized telomere repeats via telomerase reactivation. This may be one of the reasons that oesophageal SCC has a greater biological malignant potential than other tumours.

The detection of telomerase activity in normal tissue may have been attributable to lymphocytes and stem cells in the basal cell layer. However, telomerase activity was not detected in 45 (90 per cent) of 50 normal tissue samples and there was no difference between telomerase-positive and telomerase-negative normal tissue with regard to the number of lymphocytes in the normal epithelial region. Moreover, in four of the five telomerase-positive normal tissues, cancer cells infiltrating blood or lymphatic vessels of the mucosal or submucosal layer in the normal epithelial region were detected on detailed histopathological examination, compared with only three in 45 telomerase-negative normal tissues. The evidence strongly suggests that microinvasion of cancer cells was responsible for the positive activity in normal tissues. The vascular permeability of cancer cells in such patients was considered to be very high. In fact, distant organ metastasis was present in four of the five patients with telomerase-positive normal tissue, but in only three of the 45 with telomerase-negative normal tissue.

Telomerase activity in normal epithelial regions may predict occult microinvasion and correlated closely with clinical characteristics such as postoperative recurrence. Telomerase activity in normal epithelial regions may thus be a useful prognostic factor in patients with oesophageal SCC.

Telomerase activity could be used before operation to define appropriate treatment for a patient with oesophageal SCC. If telomerase activity was detected in biopsy samples of normal epithelial regions obtained from a patient with oesophageal SCC by preoperative endoscopic examination, the patient might be at high risk of metastases and could benefit from a combination of radical lymph node dissection and adjuvant systemic chemotherapy.

Telomerase activity in normal epithelial regions seems to reflect microinvasion of cancer cells through blood vessels or lymphatic vessels and could be a useful prognostic factor in oesophageal SCC. In addition, telomerase activity in normal epithelial regions may assist in selecting the appropriate treatment for patients with oesophageal SCC.

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Original article

Impaired healing of extraperitoneal intestinal anastomoses

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Background: The extra-anatomical position of a cervical oesophagogastrostomy might be a reason for impaired anastomotic healing.

Methods: This hypothesis was tested in a rat model. Jejunal resection with an end-to-end jejunojejunostomy was placed intra-abdominally in group 1 ($n = 24$) and subcutaneously in group 2 ($n = 30$). Jejunum without anastomosis was placed subcutaneously in group 3 ($n = 12$). After 3, 7 or 14 days the rats were killed; the bursting pressure of the anastomosis or jejunum was measured and the hydroxyproline level was determined.

Results: Two of 24 rats in group 1 and eight of 30 in group 2 died following anastomotic leakage (P not significant) and were excluded from other measurements. Bursting pressure was decreased after 3 days in group 1 (mean(s.e.) 62(10) mmHg) and group 2 (57(10) mmHg) compared with that in group 3 (204(17) mmHg) ($P < 0.001$). After 7 days, it was in the normal range in group 1 (200(14) mmHg), but lower in group 2 (104(15) mmHg) compared with that in group 3 (230(8) mmHg) ($P < 0.001$). Differences in hydroxyproline levels were not statistically significant between the groups after 3, 7 and 14 days.

Conclusion: Healing of jejunojejunostomies is impaired in an extraperitoneal position compared with an intra-abdominal position.

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Introduction

Resection of the oesophagus and replacement by the stomach with a cervical anastomosis is a standard procedure in the surgical treatment of oesophageal carcinoma. Leakage and stricture of the cervical oesophagogastrostomy occur in 5–26 and 7–40 per cent of patients respectively[1–3].

Intrathoracic oesophagogastric anastomoses have a much lower incidence of impaired healing compared with cervical anastomoses. Despite this inferior healing, cervical anastomoses are preferred because leakage of an intrathoracic anastomosis is associated with a high mortality rate[4–6].

Reduced blood supply to the anastomotic region following construction of a gastric tube is one of the risk factors in impaired healing of the cervical oesophagogastrostomy, but other factors must be involved[3,7]. One may be the absence of intrathoracic (or intra-abdominal) factors such as surrounding mesothelium. The hypothesis that intra-abdominal (or intrathoracic) factors affect intestinal anastomotic healing was tested in a rat model by comparing healing of small bowel anastomoses placed in the abdominal cavity and in a subcutaneous position.

Materials and methods

Sixty-six Utrecht : Wistar Unilever adult rats (33 males; sexes equally divided in groups 1–3), weighing 300–350 g, were used. They were fed a standard diet (Hope Farms, Woerden, The Netherlands) and allowed water *ad libitum*. One day before and 2 days after operation, solids were withheld and drinking water was replaced by a solution of 2·5 per cent glucose in 0·9 per cent sodium chloride. The animals received 0·9 per cent sodium chloride 20 ml/kg subcutaneously after operation to compensate for intra-operative fluid losses. Group 1 consisted of 24 rats which had a jejunojejunostomy placed intra-abdominally. Group 2 comprised 30 rats which had a jejunojejunostomy placed subcutaneously. Group 3 consisted of 12 rats which had a loop of jejunum without an anastomosis placed subcutaneously (*Fig. 1*). The groups were divided into three subgroups, with rats killed after 3, 7 or 14 days.

Severe anastomotic leakages were detected macroscopically on autopsy that was performed when a rat was

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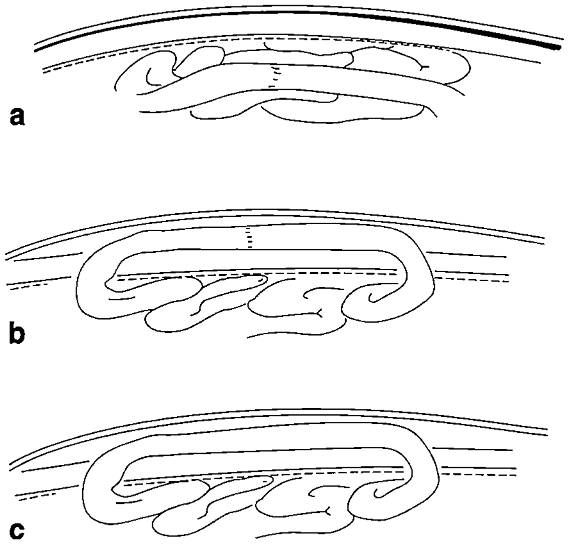

Fig. 1 The three different operative techniques: **a** intra-abdominal jejunojejunostomy (group 1), **b** subcutaneous jejunojejunostomy (group 2) and **c** normal jejunum subcutaneously (group 3)

moribund or dead before the end of the experiment. These rats were not included in the assessment of bursting pressure of the anastomosis or measurement of collagen content by determining hydroxyproline content. The rats were weighed before operation and just before death.

To evaluate whether the subcutaneous position influenced the vascularization of the jejunal segment, microangiography was performed in 12 rats that had intra-abdominal and subcutaneous jejunal loops without an anastomosis. Angiography was done after 3, 7 and 14 days, using jugular vein cannulation and perfusion with barium contrast medium under a constant pressure of 100 mmHg for 5 min. Perfusion of the vascular arcade along the bowel and the small vessels supplying the extra-abdominal intestinal segment was assessed qualitatively by two independent investigators.

Operative procedures

The rats were anaesthetized by intraperitoneal diazepam 2·5 mg/kg, intramuscular fentanyl 0·1 mg/kg, intramuscular fluanisone 5 mg/kg and subcutaneous atropine 0·05 mg/kg. After the abdominal skin had been shaved and disinfected, a 4-cm midline abdominal incision was made. One centimetre of small bowel, approximately 20 cm from the start of the jejunum, was resected and stored at −20°C to serve as a reference sample. A single-layer end-to-end anastomosis was constructed microsurgically, with a standardized continuous suture using 8/0 Vicryl (Ethicon, Norderstedt, Germany); only one straight artery was ligated in this procedure. In group 1 rats, the anastomosis was replaced intra-abdominally, and the fascia was closed with a continuous 5/0 Vicryl suture and the skin with 4/0 interrupted polyamide.

In group 2, the intestinal loop containing the anastomosis was placed subcutaneously through the midline incision, after formation of a subcutaneous pocket. The abdominal wound was closed except for the site where the loop was placed extra-abdominally and the skin was closed as in group 1. Rats in group 3 were subjected to the same procedure as those in group 2 except an anastomosis was not performed (*Fig. 1*).

After death, the anastomosis or normal subcutaneous jejunum was identified. Adhesions were cut as far from the small bowel as necessary in order not to injure the intestine and anastomosis.

Bursting pressure

A 6-cm segment containing the anastomosis was resected for bursting pressure measurements. The intestinal segment was gently flushed with 0·9 per cent sodium chloride and connected to an infusion pump on one side and a manometer on the other. Subsequently, intraluminal pressure was gradually increased by pumping 0·9 per cent sodium chloride solution containing blue dye at a rate of 2 ml/min into the segment. The pressure was recorded and sudden loss of pressure was taken as indication of leakage. The site of leakage, whether or not at the anastomosis, could easily be detected visually. Thereafter, a 1-cm segment containing the anastomosis was collected and stored at − 20°C for subsequent hydroxyproline assay.

Hydroxyproline content

Lyophilized intestinal tissue samples were digested with acid and, after neutralization, the hydroxyproline content was measured with the hypronosticon-R test[8,9]. In each rat, both the specimen resected at operation and the sample containing the anastomosis collected when the rat was killed 3, 7 or 14 days after surgery were assayed for hydroxyproline content (microgram per milligram dry weight). The difference between the sample containing the anastomosis and the reference value was obtained to quantify changes in collagen content around the anastomosis. In group 3 an intra-abdominal segment of the normal intestine was used as reference and compared with a sample of the normal jejunum that was placed subcutaneously.

Statistical analysis

Results of bursting pressure and changes in hydroxyproline content were evaluated statistically by two-way analysis of variance[10]. Differences in anastomotic leakage between groups were compared using the χ^2 test with Yates' correction. Data are given as mean(s.e.). $P \leq 0{\cdot}05$ was considered statistically significant.

Results

By 3 days after operation the rats had lost 7, 10 and 6 per cent of their weight in groups 1, 2 and 3 respectively. After 7 days weight losses were still 4, 8 and 2 per cent. Preoperative weight was almost restored after 14 days. Weight losses were not significantly different between the groups.

In group 1, two of 24 rats were dying or dead before the end of the experiment (3–10 days after operation) because of severe anastomotic leakage, compared with eight of 30 in group 2 (P not significant). Twenty-two rats in group 1 and 22 in group 2 were included for bursting pressure and hydroxyproline measurements.

Bursting pressures measured in the three groups at 3, 7 and 14 days after operation are shown in *Table 1*. On day 3, bursting pressure was significantly lower in groups 1 and 2 than in group 3 ($P < 0{\cdot}001$). Seven days after operation bursting pressure was in the normal range in group 1, but significantly lower in group 2 compared with that in controls ($P < 0{\cdot}001$). Fourteen days after operation, bursting pressures in the three groups were similar.

At 3 days, and in the majority of rats in group 2 after 7 days, the site of leakage following the bursting pressure measurement was within the anastomosis. The jejunal segment burst outside the anastomosis in all but one of the rats in group 1 killed at 7 days and in all rats of both groups after 14 days (*Table 2*).

Changes in collagen content at 3, 7 and 14 days after operation are shown in *Table 3*. Three days after operation, the hydroxyproline content of the segments containing the anastomosis decreased compared with their reference segments in groups 1 and 2, but not in group 3 (P not significant). After 7 days the hydroxyproline concentration increased above reference levels in group 1 and was almost equal to reference levels in groups 2 and 3 (P not significant). The hydroxyproline content tended to be higher after 14 days than after 7 days in all three groups (P not significant).

In the 12 rats with intra- and extra-abdominal intestinal loops, microangiography did not demonstrate any differences in perfusion of the vascular arcade along the bowel and the vessels supplying the extra-abdominal intestine at 3, 7 and 14 days. Furthermore, there were no clinical signs of ischaemia or intestinal obstruction at the site of the abdominal wall after death of the rats with an extra-abdominal loop.

Table 1 Bursting pressure of jejunojejunostomies

	Bursting pressure (mmHg)		
Group	Day 3	Day 7	Day 14
1	62(10)*	200(14)	214(16)
2	57(10)*	104(15)*	209(14)
3	204(17)	230(8)	224(8)

Values are mean(s.e.). Group 1, intra-abdominal anastomoses, group 2, subcutaneous anastomoses; group 3, normal jejunum subcutaneously
*$P < 0{\cdot}001$ *versus* group 3 (two-way analysis of variance)

Table 2 Site of leakage following bursting pressure measurements

	Time after operation (days)		
	3	7	14
Group 1			
Anastomosis	8	1	0
Other site	0	6	7
Group 2			
Anastomosis	8	5	0
Other site	0	2	7

Group 1, intra-abdominal anastomoses; group 2, subcutaneous anastomoses

Table 3 Changes in hydroxyproline content around jejunojejunostomies

	Hydroxyproline (µg/mg)		
	Day 3	Day 7	Day 14
Group 1			
Reference	3·3(0·5)	2·1(0·5)	2·6(0·3)
Anastomosis	2·0(0·5)	4·5(1·8)	5·9(1·0)
Difference	–1·3(1·1)	2·4(1·0)	3·3(1·0)
Group 2			
Reference	3·2(0·8)	3·2(0·9)	2·6(0·5)
Anastomosis	2·1(1·0)	3·3(0·6)	4·3(1·0)
Difference	–1·1(1·0)	0·1(1·1)	1·7(1·0)
Group 3			
Intra-abdominal	4·1(1·2)	2·1(1·2)	3·4(1·4)
Subcutaneous	4·1(1·2)	2·2(0·5)	4·7(2·4)
Difference	0·0(1·2)	0·1(1·1)	1·3(1·2)

Values are mean(s.e.). Group 1, intra-abdominal anastomoses; group 2, subcutaneous anastomoses; group 3, normal jejunum subcutaneously. Changes in collagen content are expressed as differences between hydroxyproline values found in the reference segments and values found after 3, 7 or 14 days. There were no significant differences

Discussion

The healing of a cervical oesophagogastrostomy is frequently impaired and some anastomotic complications can be explained by poor blood flow in the gastric tube[3,4,11].

The position of the anastomosis might affect its healing, and this hypothesis was tested in a rat model. Severe anastomotic leaks occurred more frequently in rats with extra-peritoneal anastomoses and after 7 days the bursting pressure of subcutaneous anastomoses was significantly lower than that of intra-abdominal anastomoses. The site of leakage was outside the anastomosis in most of the intra-abdominal anastomoses and within the anastomosis in most of the subcutaneous anastomoses (*Tables 1* and *2*).

This parallels the data on hydroxyproline content in *Table 3*. After an initial decrease below reference level, the hydroxyproline content of the subcutaneous anastomoses had returned to reference values after 7 days, while the content of the intra-abdominal anastomoses had surpassed the reference level, suggesting that the anastomoses were stronger than the other parts of the intestine.

When considering absolute values, the actual anastomotic hydroxyproline content may be affected by non-anastomotic tissue in that segment. Hydroxyproline content should not be related directly to tissue strength and to healing, because this will depend on the degree of cross-linking of collagen strands. In a state of active collagen metabolism, as can be expected after surgery, the degree of cross-linking may vary during the healing process[12]. In the present study the hydroxyproline data, although only an indirect and crude representation of collagen strength, support the data on leakage rates and bursting pressure.

Changes in weight were not significantly different between the groups, which probably excludes malnutrition as a reason for differences in anastomotic healing[13].

No impaired vascularization of the extra-abdominal loop was shown at microangiography and no clinical signs of ischaemia or obstruction at the site of the abdominal wall were seen. These findings support the assumption that no obstruction or tension at the abdominal wall compromised the vascularization or patency of the extra-abdominal loop, as is occasionally experienced in clinical practice after performance of an ileostomy.

It therefore seems that the environment interferes with the healing of anastomoses and it may well be that mesothelial cells cover an anastomosis and provide sealing. Also, mesothelial membranes are known to be active in transporting fluids and solutes between the body cavities and the circulation. Furthermore, mesothelium plays a role in chemotaxis which is a step in removal of tissue debris after local trauma[14]. Mesothelial cells can produce growth factors which may also have a beneficial effect on anastomotic healing[15–17]. For these reasons anastomotic healing in the abdominal cavity is likely to take place as primary intention. In a subcutaneous pocket, more dead space is present and the potential for debridement by the mesothelium is absent[18]. There is no mesothelial (abdominal or pleural) fluid providing inflammatory cells, growth factors and maybe nutrients[19–21]. Intestinal anastomoses surrounded by mesothelium, pleura, peritoneum or even pericardium, seem to heal better than anastomoses that are positioned outside these membranes[22–24].

Small bowel anastomoses in their physiological location surrounded by mesothelium heal better than extraperitoneal anastomoses.

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Original article

Clinical evaluation of lymph node metastasis in gastric cancer defined by the fifth edition of the TNM classification in comparison with the Japanese system

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Background: This study compared the classification of lymph node metastasis according to the number of involved nodes based on the new tumour node metastasis (TNM) system (fifth edition) with the classification by the Japanese Research Society for Gastric Cancer from an anatomical perspective.

Methods: The two classifications were related to long-term results in 1489 patients with gastric cancer who underwent gastrectomy with systematic extended lymphadenectomy.

Results: Both classifications performed well as prognostic indicators (5-year survival rates: pathological (p) N_0, 89 per cent; pN_1, 66 per cent; pN_2, 34 per cent; pN_3, nil; and M_1, 10 per cent by the TNM classification; n0, 89 per cent; n1, 63 per cent; n2, 46 per cent; n3, 20 per cent; and n4, 8 per cent by the Japanese classification). For regional lymph nodes, the TNM classification was a better index of the prognosis. Significant survival differences were observed among patients with M_1 disease according to the number of involved lymph nodes (between one and six nodes, 48 per cent; seven to 15 nodes, 12 per cent; more than 15 nodes, 2 per cent), indicating that patients with distant metastatic lymph nodes (M_1) should also be classified by the number of involved nodes. On the other hand, the Japanese classification has the added benefit of being a good indicator of the anatomical extent of lymphadenectomy.

Conclusion: The new TNM classification provided a better index of the prognosis of patients who underwent systematic lymph node dissection. However, both classifications have specific benefits in the surgical treatment of gastric cancer.

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Introduction

The benefits of systematic extended lymphadenectomy (the so-called Japanese-style lymphadenectomy) for gastric cancer have been reported in Western countries as well as in Japan in recent years[1,2], although it was reported that the operative mortality rate and incidence of complications for Japanese-style lymphadenectomy were higher than those for dissection of perigastric lymph nodes only[3].

The classification established by the Japanese Research Society for Gastric Cancer (JRSGC)[4] of the extent of lymph node metastasis, an indicator of Japanese-style lymphadenectomy, is widely known. The grading of lymph node metastasis using the previous tumour node metastasis (TNM) classification (fourth edition)[5] was based on the anatomical sites of metastatic lymph nodes as in the JRSGC system. However, comparative evaluations of the extent of lymph node metastasis have been difficult because of the difference in the anatomical borders for the lymph node groups between these two systems.

With the new TNM classification (fifth edition)[6], the grade of lymph node metastasis in gastric cancer is categorized according to the number of involved lymph nodes. This new classification is expected to become a global standard.

The purpose of the present study was to evaluate the prognostic significance in gastric cancer of the grade of lymph node metastasis defined by the new TNM classification in comparison with the extent of lymph node metastasis defined by the Japanese classification.

Patients and methods

The study group comprised 1489 Japanese patients (1004 men, mean age 58·8 years; 485 women, mean age 56·6 years) who underwent gastrectomy with systematic

Table 1 Relationship between the classification of lymph node metastasis in patients with gastric cancer by the tumour node metastasis and Japanese systems

	pN_0	pN_1	pN_2	pN_3	M_1	pN_x	Total
n0	801	0	0	0	0	78	879
n1	0	218	41	2	0	0	261
n2	0	101	70	23	0	0	194
n3	0	10	16	10	34	0	70
n4	0	0	0	0	85	0	85
Total	801	329	127	35	119	78	1489

lymphadenectomy for gastric cancer between August 1978 and December 1996. In all cases, lymph node metastasis was examined histologically and the extent of the metastasis was determined according to the Japanese classification[4]: n0, no lymph node metastasis; n1, metastasis to the first-tier lymph node group; n2, metastasis to the second-tier lymph node group; n3, metastasis to the third-tier lymph node group; and n4, metastasis to the fourth-tier lymph node group. The grade of lymph node metastasis was also determined according to the new pathological (p) TNM classification (fifth edition)[6]: pN_0, cases without lymph node metastasis in which 15 nodes or more are examined histologically; pN_1, between one and six involved regional lymph nodes; pN_2, seven to 15 involved regional lymph nodes; pN_3, 16 or more involved regional lymph nodes; and M_1, distant lymph node metastasis. The definition of 'regional lymph nodes' in the new TNM classification[6] is as follows: the perigastric nodes along the lesser and greater curvatures, the nodes along the left gastric, common hepatic, splenic and coeliac arteries, and the hepatoduodenal nodes. The involvement of other intra-abdominal lymph nodes such as retropancreatic, mesenteric and para-aortic nodes is classified as distant metastasis. The histological cancerous depth of invasion was determined according to the TNM classification (fifth edition).

According to the depth of invasion, there were 684 patients with tumour *in situ* (T_{is}) and pT_1, 325 with pT_2, 408 with pT_3 and 72 with pT_4.

The extent of lymph node dissection was D_{0-1} in 216, D_2 in 210, D_3 in 801 and D_4 in 262 patients. D_{0-1} or D_2 lymphadenectomy was mainly performed for early gastric cancer, D_3 lymphadenectomy for advanced gastric cancer and D_4 lymphadenectomy (since 1989) for advanced gastric cancer with N_2 or more macroscopic lymph node metastasis.

Follow-up ranged from 0·5 to 16·5 (mean 4·5) years. Cumulative survival rates were calculated with the Kaplan–Meier method[7] and compared with the log rank test. The significance of differences in the number of dissected lymph nodes was determined by Student's *t* test. $P < 0.05$ was considered significant.

Results

The number of patients classified by both classifications and the relationship between n numbers and pN numbers are shown in *Table 1*.

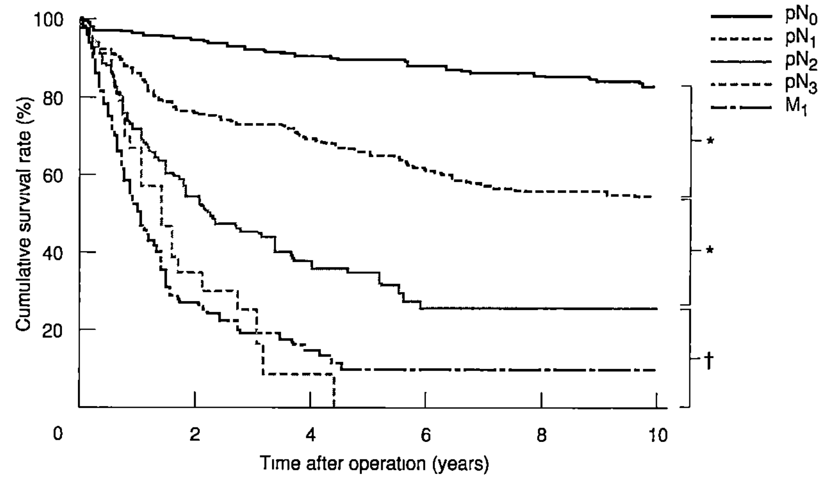
The mean(s.d.) number of removed lymph nodes according to the extent of the lymph node dissection was 23·0(13·1) in D_{0-1}, 35·7(21·4) in D_2, 42·0(17·0) in D_3 and 56·2(20 0) in D_4 lymph node dissection. There was a significant difference in the number of dissected lymph nodes among these groups ($P < 0.0001$).

Long-term results according to the degree of lymph node metastasis

There were significant differences in survival depending on the grade of lymph node metastasis by the TNM classification; the cumulative 5-year survival rate was the best in the pN_0 group (89 per cent), followed by the pN_1 (66 per cent), pN_2 (34 per cent) and pN_3 (no survivors) groups. However, there was no significant difference between the pN_3 and M_1 (10 per cent) groups (*Fig. 1*). When based on the extent of lymph node metastasis by the Japanese classification, the cumulative 5-year survival rate was the best in the n0 group (89 per cent), followed by the n1 (63 per cent), n2 (46 per cent), n3 (20 per cent) and n4 (8 per cent) groups (*Fig. 2*).

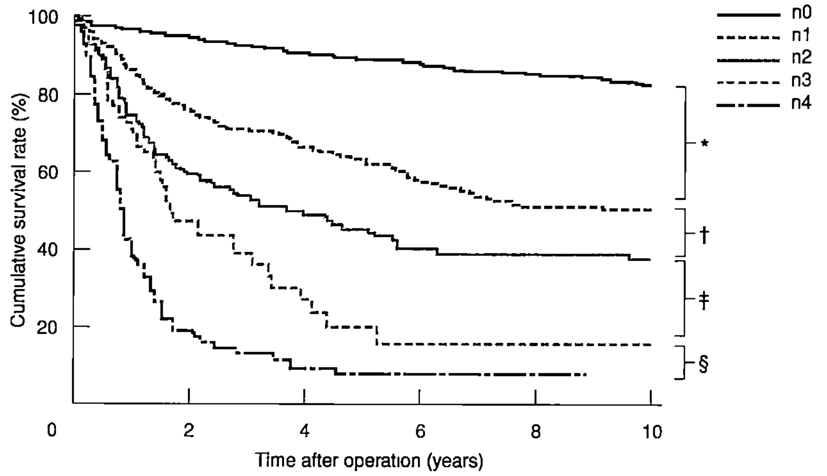
Comparison of Japanese and tumour node metastasis systems

There were no significant differences in long-term survival when each pN group was subdivided according to the extent of lymph node metastasis by the Japanese classification. All patients with n4 and most patients with n3 disease by the Japanese classification were classified into M_1 by the TNM system. Long-term survival according to the grade of lymph node metastasis



No. at risk						
pN$_0$	801	680	545	425	318	224
pN$_1$	329	220	165	121	95	73
pN$_2$	127	55	26	13	11	5
pN$_3$	35	7	1			
M$_1$	119	25	10	5	4	1

Fig. 1 Survival of patients with gastric cancer (n = 1489) according to the degree of lymph node metastasis by tumour node metastasis (TNM) classification. *P < 0·0001, †P = 0·013 (log rank test)



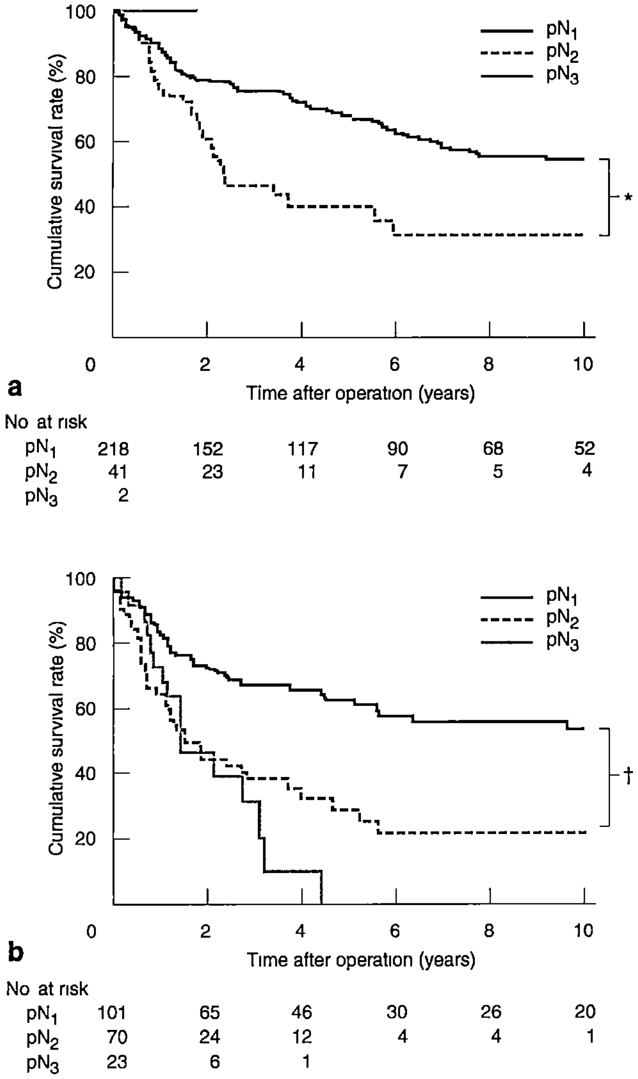
No. at risk						
n0	879	748	581	442	330	230
n1	261	178	130	98	73	55
n2	194	96	60	35	30	12
n3	70	27	9	3	3	2
n4	85	13	6	4	1	

Fig. 2 Survival according to the extent of lymph node metastasis by the Japanese classification. *P < 0·0001, †P = 0·0005, P = 0·013, §P = 0·0002 (log rank test)

by the TNM classification in patients with n1 or n2 nodes by the Japanese classification varied significantly (*Fig. 3*). Of the 261 patients with n1 lymph node metastasis, the cumulative 5-year survival rate of the 218 patients with pN$_1$ metastasis (68 per cent) was significantly better than that of the 41 with pN$_2$ disease (41 per cent) by the TNM classification. Of the 194 patients with n2 lymph node metastasis, the cumulative 5-year survival rates in those with pN$_1$, pN$_2$ and pN$_3$ nodes were 63 per cent, 29 per cent and nil (*Fig. 3*).

Number of involved nodes in patients with distant node metastasis

There were significant differences in long-term survival according to the total number of involved lymph nodes in



a

No at risk

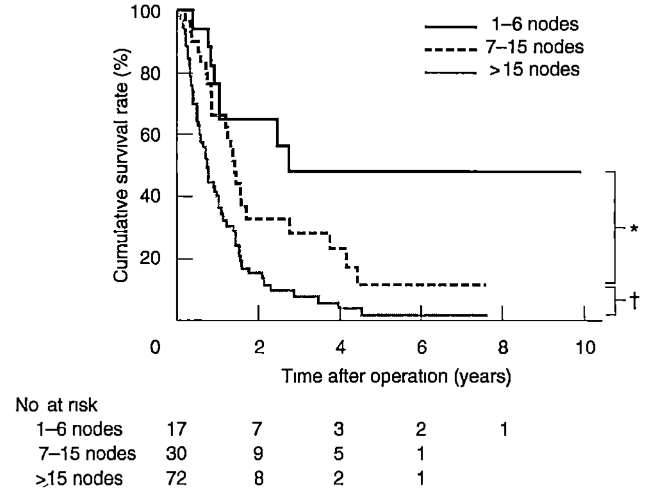
	0	2	4	6	8	10
pN1	218	152	117	90	68	52
pN2	41	23	11	7	5	4
pN3	2					

b

No at risk

	0	2	4	6	8	10
pN1	101	65	46	30	26	20
pN2	70	24	12	4	4	1
pN3	23	6	1			

Fig. 3 Survival according to n number in patients with lymph node metastasis. **a** Patients with metastasis to group 1 (n1) lymph nodes. **b** Patients with metastasis to group 2 (n2) lymph nodes. $^*P = 0{\cdot}002$, $^\dagger P < 0{\cdot}0001$ (log rank test)



No at risk

	0	2	4	6	8
1–6 nodes	17	7	3	2	1
7–15 nodes	30	9	5	1	
>15 nodes	72	8	2	1	

Fig. 4 Long-term results according to the total number of involved nodes located far from the regional lymph node (M_1 group). $^*P = 0{\cdot}07$, $^\dagger P = 0{\cdot}003$ (log rank test)

patients with distant lymph node metastasis (M_1) in the abdominal cavity (*Fig. 4*). The cumulative 5-year survival rates were 49 per cent for patients with between one and six involved lymph nodes, 12 per cent for those with between seven and 15 nodes, and 3 per cent for those with more than 15 involved nodes.

Discussion

Lymph node metastasis is an important prognostic factor in patients with gastric cancer. Several Japanese surgeons have reported the effectiveness of systematic extended lymphadenectomy for patients with gastric cancer[8–10]. However, the results from Japan were slow to be accepted in Western countries because the classification of lymph node metastasis is different. Moreover, because of the findings from a randomized trial that the operative mortality rate and incidence of complications for Japanese-style lymphadenectomy were higher than those for the Western-style operation[3], the Japanese-style dissection was not accepted worldwide. Recently, however, reports[1,2] from Western countries, which were based on the Japanese classification of lymph node metastasis, have approved systematic extended lymphadenectomy because of the favourable outcome after surgery.

In the present study, both the TNM and Japanese systems were found to be good indicators of the prognosis of gastric cancer. However, the further discrimination provided by the pN number of the TNM classification in subjects with the same n number by the Japanese classification indicates that the prognosis of gastric cancer is more closely associated with the number of metastatic regional lymph nodes than with the anatomical position of lymph node metastasis.

There was no significant difference between the prognosis of patients with M_1 and pN_3 disease. However, there were significant differences in the long-term outcome related to the number of involved lymph nodes, suggesting that the pN category for regional lymph node metastasis can be extended to include patients with M_1 lesions. However, even when the total number of involved lymph nodes was the same, the prognosis of patients with distant lymph node metastasis was worse than that of those without such metastasis. This suggests that the number of involved distant lymph nodes is a more important prognostic factor than the number of involved regional lymph nodes. This is supported by the observation of a significant difference in prognosis between patients with n3 and n4 disease in those with M_1 nodal metastases.

Concerning the problems of TNM classification, when the number of dissected lymph nodes was less than 15, the case was classified as pN_x, regardless of the extent of lymph node metastasis. In the present study, although the number of dissected lymph nodes was more than 15 in most patients even with D_{0-1} resection, 9 per cent of the patients with n0 disease were classified as pN_x, and most of these patients were treated to a limited extent by surgery[11]. The number of pN_x cases may increase in future, because the incidence of early gastric cancer is increasing in Western countries as well as in Japan[12–14].

Another problem of the TNM classification may be the lack of an indicator for the extent of lymph node dissection during surgery, because intraoperative macroscopic evaluation of the number of involved lymph nodes is difficult[15–17]. In contrast with the TNM system, in the Japanese system n1, n2, etc. indicate the macroscopic level of involvement, whereas D_1, D_2, etc. indicate the extent of lymph node dissection. Most of the patients in this study were subjected to systematic lymphadenectomy based on the Japanese classification.

In conclusion, the category of lymph node metastasis based on the TNM system (fifth edition) rather than the Japanese classification proved to be a better indicator with respect to the prognosis of patients with gastric cancer who underwent systematic lymphadenectomy. However, the M_1 category for distant lymph node metastasis may not be necessary. Concerning the therapeutic use of these classification systems, the Japanese system is useful for establishing the anatomical extent of lymph node dissection during surgery, while the TNM classification lacks indicators for the extent of lymphadenectomy. Thus, the classifications have separate benefits and should be used simultaneously for treatment of gastric cancer.

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Vascular Surgical Society of Great Britain and Ireland

The following abstracts are from the papers presented to the 32nd Annual Conference of the Vascular Surgical Society of Great Britain and Ireland, held in Hull, UK, on 18–20 November 1998. President of the Society, Mr J. M. D. Galloway, was in the Chair.

Twenty-three years of experience of carotid endarterectomy

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Background: Carotid endarterectomy (CEA) has been an evidence-based treatment for symptomatic severe carotid stenosis since 1991. Surgical techniques and patient selection have changed over the years. The results of CEA in a single centre over a 23-year period were reviewed.

Methods: Prospectively gathered preoperative, operative, postoperative and long-term follow-up data were analysed. Routine intraoperative shunting and patch closure has been used since 1988. Data were analysed using the χ^2 test or by logistic regression, adjusting for age at operation and date of operation.

Results: Five hundred and seventy-three CEAs (37 bilateral and three repeat procedures) were carried out on 533 patients. Trainees performed an increasing proportion of CEAs from 1996 to 1998 (15, 50 and 56 per cent respectively). The perioperative death rate was 0·8 per cent and the rate of any perioperative neurological deficit was 6·9 per cent. Other causes of morbidity included nerve injury (5·1 per cent) of which the commonest was to the hypoglossal nerve (2·7 per cent). During follow-up (median 4 (range 0–22) years) there were 81 neurological events (15·9 per cent) which included 35 ipsilateral (6·6 per cent) and 18 contralateral (3·4 per cent) strokes. There was no significant difference in outcome for grade of surgeon, intraoperative shunting or patch closure. Major causes of death were cardiac death (74; 14·6 per cent) followed by stroke (23; 4·5 per cent) and cancer (20; 3·9 per cent).

Conclusion: The introduction of routine intraoperative shunting and patch closure, as well as allowing surgical trainees to perform supervised CEAs, has not affected perioperative morbidity and mortality rates or long-term outcome.

Audit of surgical technique during carotid endarterectomy by intraoperative duplex ultrasonography: trainees compared with consultant

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Background: There has been increasing interest in audit of outcome following surgery. A previous study reported a significant difference in clinical outcome between consultant and trainees but there is no information on technical factors. Duplex ultrasonography before wound closure was used to compare clinical and technical outcome for consultant and trainees.

Methods: Patients underwent endarterectomy (89 by consultant, 60 by six trainees). In the consultant group nine vessels were patched and 36 patients underwent shunting compared with seven and 31 respectively for trainees.

Results: In the consultant group there were two deaths, one stroke, one transient ischaemic attack (TIA) and two cranial nerve injuries. The neurological event rate was 2 per cent, and overall stroke and death rate 3 per cent. There were ten residual flaps (11 per cent) (three re-explored) and eight kinks (9 per cent). The residual stenosis rate was 10 per cent (nine of 89) and following re-exploration this reduced to 7 per cent. In the trainee group there was one death, two strokes, one TIA and one cranial nerve injury. The neurological event rate was 5 per cent, and the overall stroke and death rate 3 per cent. There were nine flaps (15 per cent) (four re-explored) and 13 kinks (22 per cent). The residual stenosis rate was 22 per cent (13 of 60) which reduced to 15 per cent (nine of 60) following re-exploration. There was no significant difference in clinical outcome between consultant and trainees but there was an increased incidence of technical problems among the trainees ($t = 2{\cdot}12$, $P < 0{\cdot}05$).

Conclusion: Intraoperative duplex ultrasonography is a valuable method for assessing surgical technique; it gives immediate feedback to the surgeon, enables corrective measures to be taken and may facilitate training.

Carotid angiography is used more selectively in the Asymptomatic Carotid Surgery Trial

P. Robless and A. Halliday on behalf of the Asymptomatic Carotid Surgery Trial collaborators

Background: The ongoing Asymptomatic Carotid Surgery Trial (ACST) has randomized more than 1900 patients to determine whether carotid endarterectomy prolongs stroke-free survival compared with best medical treatment alone. Previously the Asymptomatic Carotid Atherosclerosis Study demonstrated that preoperative angiography caused stroke or death in 1 per cent of patients, and many centres have now reduced or abandoned this practice. This study determined the changing practice of carotid angiography in the ACST.

Methods: Collaborating surgeons completed questionnaires annually on their use and method of angiography. Information on patients in the ACST who had angiography at randomization was also obtained.

Results: In 1993, 77 per cent of responding collaborators always performed preoperative angiography and 23 per cent used angiography selectively. This trend has reversed: by 1997, 26 per cent always used preoperative angiography, 70 per cent of respondents used preoperative angiography selectively and 4 per cent had abandoned angiography ($P < 0{\cdot}001$, χ^2 for trend). Information on carotid angiography at randomization has to date been obtained on 1141 patients in the ACST. Some 44 per cent (497 of 1141) had carotid angiography at randomization. Surgical patients had angiography more commonly than those in the medical group (49 *versus* 42 per cent; $P < 0{\cdot}03$, χ^2 test). Changes in carotid angiography were analysed by year of randomization. In 1993, 61 per cent of patients randomized had carotid angiography compared with 42 per cent in 1996 and 1997 ($P < 0{\cdot}001$, χ^2 for trend). The use of carotid angiography was not related to degree of stenosis estimated by Doppler ultrasonography.

Conclusion: In the ongoing ACST, there is increasingly selective use of carotid angiography. Less than half the patients in this study had carotid angiography and the use of angiography is now decreasing. This has important implications for validation of carotid duplex in this trial and in future studies.

Thrombelastography can differentiate ischaemic from haemorrhagic stroke

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Background: Thrombolysis could be a major step forward in the treatment of acute ischaemic stroke. Early treatment is essential to maximize therapeutic benefit. Imaging by computed tomography (CT) or magnetic resonance imaging is mandatory to exclude haemorrhagic stroke before initiation of therapy. Thrombelastography (TEG), a test of global haemostasis, produces a characteristic tracing over 15–30 min. The potential of TEG to differentiate patients with ischaemic from haemorrhagic stroke was investigated.

Methods: Fifteen patients with a clinical diagnosis of acute stroke were studied. Fibrinogen levels and lipid profiles were measured, and CT of the brain, coagulation screens and TEG were performed. The CT scans were interpreted by a single radiologist. TEG data were classified as normal (index less than 2), hypercoagulable (index 2–3) or profoundly hypercoagulable (index greater than 3).

Results: There was no correlation between any of the parameters studied other than TEG with CT findings. Both patients with a haemorrhagic stroke showed normal findings on TEG. Eleven of the 12 patients with ischaemic stroke were hypercoagulable or profoundly hypercoagulable.

	TEG report		
CT report	Normal	Hyper-coagulable	Profoundly hypercoagulable
Ischaemic stroke	1	7	4
Haemorrhagic stroke	2	0	0
Cerebral metastases	0	1	0

Conclusion: TEG is capable of differentiating haemorrhagic from ischaemic stroke. It has the potential to target thrombolytic therapy for those patients most likely to benefit.

Impact of spontaneous embolization on cognitive function

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Background: Although microembolization may not be associated with focal neurological events following carotid endarterectomy (CEA), it might contribute towards cognitive impairment.

Methods: Forty-nine patients undergoing CEA underwent 30 min of preoperative ipsilateral transcranial Doppler (TCD) monitoring and a battery of tests of cognitive function, and the results were compared with those of age-matched normal controls.

Results: Seven patients who were spontaneously embolizing had significantly worse preoperative cognitive function scores than 42 patients with no recorded emboli ($P = 0{\cdot}03$). Overall, patients undergoing CEA had a significant cognitive deficit compared with age-matched normal controls.

	No emboli ($n = 42$)		Emboli ($n = 7$)	
Attention	79	81	73	73
Memory	87	83	74	73
Language	84	85	77	92
Visuospatial	81		76	

Values are scores for patients undergoing CEA expressed as a percentage of those for age-matched normal controls. Different values were obtained as a result of using different tests. $P = 0{\cdot}03$ (emboli *versus* no emboli)

Conclusion: Patients who have evidence of spontaneous preoperative embolization on TCD monitoring have a greater degree of preoperative cognitive impairment. This finding underlines the potential clinical importance of microembolization and suggests that this phenomenon should be investigated further.

Re-evaluation of criteria for reoperation in carotid endarterectomy using intraoperative duplex imaging

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Background: The aim of this study was to compare data obtained during surgery with data collected at 6 weeks after operation to evaluate appropriate criteria for reoperation.

Methods: One hundred and twenty consecutive patients undergoing carotid endarterectomy had duplex scans at operation and 6 weeks later. Neurological evaluation was also documented.

Results: Of 96 patients who had a normal intraoperative duplex scan by standard criteria, 91 had normal scans at 6 weeks. One occluded an internal carotid artery (ICA) at 6 weeks with no symptoms. Four had kinks or high-grade contralateral lesions leading to velocity enhancement but no filling defect. All were asymptomatic. Twenty-four patients had abnormal intraoperative scans. Thirteen patients had visible kinking of the ICA or reperfusion hyperaemia; 12 of these patients had normal 6-week scans and one had a mild residual kink but no symptoms. Eleven patients had visible colour-filling defects and significant velocity enhancement. Nine of these were reopened and refashioned. Subsequent duplex imaging was satisfactory in all cases and 6-week scans were normal. One patient had an occluded ICA at operation and developed a dense stroke after operation. Another had residual raised velocities distally which remained at 6 weeks. This patient had no symptoms.

Conclusion: Intraoperative velocity measurements alone cannot be relied upon as an indication for reoperation. Significant velocity enhancement combined with a visible filling defect appears to represent a satisfactory criterion for reoperation. There were no complications as a result of reoperation. There was no early restenosis in the whole group and there were no neurological sequelae in any patient with a satisfactory scan using the above criteria.

Transcranial Doppler-directed dextran therapy in the prevention of postoperative carotid thrombosis

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Background: Evidence suggests that embolization precedes carotid thrombosis, a previously unpredictable event complicating 2–3 per cent of all carotid endarterectomies. It was hypothesized that dextran 40 therapy might prevent progression to complete thrombosis in high-risk patients.

Methods: Between October 1995 and July 1998, 400 consecutive patients were monitored following carotid endarterectomy using transcranial Doppler ultrasonography. Those with sustained embolization (more than 25 in 10 min) or those with emboli that distorted the middle cerebral artery waveform were commenced on an incremental dextran 40 infusion.

Results: Two hundred and sixteen patients (54 per cent) had one or more emboli detected (96 per cent within 2 h of flow restoration) but only 15 (4 per cent) required dextran therapy. Embolization ceased in each case although the dextran dose had to be adjusted in four. In one of the latter patients, embolization recurred on day 5 but was again controlled with high-dose dextran. Overall, the death and any stroke rate was 2 per cent and no patient suffered a stroke due to carotid thrombosis.

Conclusion: A few patients develop sustained embolization following carotid endarterectomy which, in previous studies, has been shown to be highly predictive of carotid thrombosis. The authors' experience to date suggests that dextran can stop this phase of embolization and prevent progression to complete carotid thrombosis. However, the dose of dextran has to be adjusted in 25 per cent of patients (i.e. blind administration of dextran may not be effective) and, very rarely, embolization may recur later.

Near-infrared spectroscopic monitoring of patients undergoing carotid endarterectomy under locoregional anaesthesia

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Background: The level of cerebral desaturation, which is associated with a change in level of consciousness during carotid endarterectomy, was measured by near-infrared spectroscopy.

Methods: Patients were recruited in two centres over 24 months. Surgery was performed under deep and superficial cervical block using 0·5 per cent bupivacaine, with temazepam as a premedication Cerebral oxygenation was measured by Critikon 2020 near-infrared spectrophotometers (Johnson and Johnson Medical, Newport, UK).

Results: Forty-nine procedures were performed on 45 patients (39 men; age range 52–84 (mean 68) years). Recordings were made from the ipsilateral frontal site in 38 patients, from the ipsilateral temporal site in 23 and bifrontally in eight patients. Monitoring failed in three subjects. Percentage changes in regional cerebral oxygen saturation are detailed below.

	Change in saturation (%)	
Site	Symptomatic ($n = 8$)	Asymptomatic ($n = 41$)
Frontal (ipsilateral)	6·4 (2·5–14)*	2·4 (0–8)*
Temporal	3·8 (2–8)*	1·5 (0–8)
Frontal (contralateral)	2 (0–4)	0·2 (0–0·5)

Values are mean (range) $^{*}P < 0{\cdot}01$

Conclusion: Significantly different levels of cerebral desaturation occur in patients with neurological compromise during carotid endarterectomy compared with those who are unaffected.

Transcranial Doppler ultrasonography as a predictor of haemodynamically significant carotid stenosis

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Background: Transcranial Doppler (TCD) ultrasonography can detect evidence of collateral flow across the anterior communicating artery and/or the posterior communicating artery, which occurs when there is significant alteration of 'inflow' to the brain. The aim of the study was to determine the blood flow velocity produced by a carotid stenosis which produces this haemodynamic effect on the cerebral circulation and evokes collateral circulation.

Methods: Forty-eight patients with varying degrees of carotid stenosis (10 per cent to occlusion) who underwent both carotid duplex and TCD examination were reviewed. An ATL HDI 3000 ultrasound system was used for the carotid and TCD studies. The carotid examination recorded peak-systolic velocity (PSV) and end-diastolic velocity (EDV) in the carotid systems bilaterally. TCD recorded Doppler spectra from the bilateral

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middle cerebral, anterior cerebral, posterior cerebral, intracranial vertebral and basilar arteries. Collateral flow was assessed in two ways: 'intracranial crossover' collateral and 'posterior to anterior' collateral. Each internal carotid artery (ICA), together with the ipsilateral hemisphere, was analysed for the presence or absence of collateral flow. Data were expressed as mean(s.e.m.).

Results: The PSV of the group with collateral circulation was 472(14) cm s^{-1} and that of the group without collateral flow was 164(3) cm s^{-1} ($P < 0{\cdot}0001$, Mann–Whitney test). The respective EDVs were 158(13) and 58(7) cm s^{-1} ($P < 0{\cdot}0001$).

Conclusion: PSVs and EDVs in the ICA, in conjunction with collateral flow measured by TCD, are indicators of a haemodynamically significant carotid lesion, and provide more information than two-dimensional imaging studies. In the future, parameters set by combining carotid duplex and TCD investigations may represent the 'gold standard' for evaluation of cerebral blood flow.

Deaths from ruptured abdominal aortic aneurysm in Wales

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Background: The aim was to determine the true incidence and operative mortality rate of patients with ruptured abdominal aortic aneurysm (AAA) who reach hospital alive in Wales.

Methods: Patients presenting with a ruptured AAA between September 1996 and August 1997 were analysed. The data were collected prospectively by an independent body, observing strict confidentiality.

Results: Two hundred and thirty-three patients with confirmed ruptured AAA were identified. One hundred and thirty-three patients (57 per cent) underwent attempted operative repair. Eighty-five (64 per cent) died within 30 days. All 100 patients who received no operation died. Of the 233 patients, 92 were admitted under vascular surgeons (VSs) and 141 under non-vascular surgeons (NVSs). VSs operated on 82 patients (89 per cent) of whom 50 (61 per cent) died; NVSs operated on 51 (36 per cent) of whom 35 (69 per cent) died.

Conclusion: This study is the only independent prospective study of death among patients with ruptured AAA who reached hospital alive. Some 57 per cent of the patients with a ruptured AAA were operated on. The operative mortality rate was 64 per cent and the overall mortality rate was 79 per cent. VSs were significantly more aggressive (89 per cent) in the management of ruptured AAA (i.e. more likely to operate) than NVSs (36 per cent) ($P < 0{\cdot}0001$). Despite this, the operative mortality rate for VSs was 61 per cent, whereas for NVSs it was 69 per cent ($P = 0{\cdot}372$). The overall mortality rate (including operated and non-operated patients) for NVSs (89 per cent) was significantly higher than that for VSs (65 per cent) ($P < 0{\cdot}0001$). In conclusion, ruptured AAA is common in Wales and associated with a high mortality rate even when managed by VSs.

Limb outcome following failed femoropopliteal polytetrafluoroethylene bypass for intermittent claudication

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Background: Femoropopliteal (FP) bypass using polytetrafluoroethylene (PTFE) is still considered by many surgeons to be a reasonable procedure for severe intermittent claudication (IC) without limb-threatening ischaemia. The consequences of FP graft failure were examined.

Methods: Over 8 years, 54 patients had 55 FP grafts (that subsequently occluded) inserted for severe IC (42 PTFE and 13 vein grafts) above (30) or below (25) the knee. There were no operative deaths. During the same interval a total of 191 FP grafts were placed, 100 of which were vein grafts. Patient demography and risk factor analysis was similar for both groups.

Results: Nineteen patients required amputation subsequent to a failed graft, all of these following PTFE grafts. Mean time to occlusion was 12·2 (range 0–79) months. For PTFE grafts, the mean(s.d.) ankle index rose from 0·51(0·14) to 0·95(0·15) after operation but fell to 0·25(0·15) after occlusion, confirming a highly significant deterioration from preoperative levels, which was not seen in vein graft occlusions.

Conclusion: Long-term FP bypass patency rates with vein are superior to those obtained with PTFE. Failed PTFE grafts show a significant deterioration in pressure indices compared with preoperative values. FP grafts for IC carry an intrinsic risk of limb loss which is much greater when vein is not used ($P < 0{\cdot}001$).

Superficial femoral angioplasty

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Background: Superficial femoral angioplasty (percutaneous transluminal angioplasty, PTA) is a widely performed therapeutic modality used throughout the UK in the treatment of intermittent claudication. However, there is still concern over its efficacy in the management of atherosclerotic occlusive disease. Long-term outcome was examined in patients undergoing PTA for short (less than 10 cm) occlusions or stenoses.

Methods: Data were collected prospectively for 413 patients undergoing femoral angioplasty and entered into a database for long-term outcome analysis. Patients were seen at 3, 6 and 12 months and at yearly intervals. Doppler ultrasonography and clinical assessment were performed in all patients and duplex imaging was carried out in those in whom there was doubt about patency. Finally, surviving patients were simply questioned as to whether they felt the original PTA to have been worthwhile.

Results: Mean follow-up time was 7 (range 2–11) years. Excluding an initial technical failure rate of 8 per cent, cumulative primary patency at 1, 2, 3, 4 and 5 years was 64, 55, 36, 21 and 14 per cent respectively. Moreover, clinical assessment revealed improvement of the presenting complaint in only 40, 29, 17, 9 and 7 per cent respectively.

Conclusion: Superficial femoral PTA does not appear to be effective in the management of intermittent claudication in most patients.

Distal venous arterialization for non-reconstructable arterial disease

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Background: Despite advances in vascular surgical and interventional radiological techniques, 14–20 per cent of patients with critical lower limb ischaemia will not be suitable for distal arterial reconstruction owing to occlusion of crural and pedal vessels. Following investigation into the venous anatomy of the foot, the disease-free venous bed was used as an alternative conduit for perfusion of peripheral tissues.

Methods: For 22 months, venous arterialization was performed for all patients with non-reconstructable disease but potentially salvageable feet. There were 15 patients; 14 had surgery for chronic ischaemia and one for acute embolization from a popliteal aneurysm after unsuccessful thrombolysis. The inflow vessel was the common femoral artery in 12 and the popliteal artery in three patients. Reversed contralateral long saphenous vein was used in five, a composite graft in three and a polytetrafluoroethylene graft with vein patch in the remaining seven. The distal anastomosis was to the dorsal venous arch (13 cases) and in two to vena comitantes of the posterior tibial vein owing to extensive tissue loss. Various techniques were employed to destroy the valve.

Results: Three procedures failed immediately after operation and major amputation was required. The remaining 12 patent grafts were monitored by duplex scan; two required intervention to correct distal anastomotic stenosis by angioplasty and atherectomy (one patient each). The limb salvage rate at 2–22 months of follow-up was 80 per cent.

Conclusion: Distal venous arterialization is a unique and promising operation which merits further evaluation.

Prospective randomized double-blind placebo-controlled crossover study to assess the effect of sublingual glyceryl trinitrate in patients with intermittent claudication

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Background: The effect of sublingual glyceryl trinitrate (GTN) on the claudication distance (CD) and maximum walking distance (MWD) of patients with intermittent claudication was assessed.

Methods: Inclusion criteria were. history of intermittent claudication; resting ankle : brachial pressure index (ABPI) of 1·00 or less; fall in ABPI of more than 0·1 following exercise; and patient not taking nitrates. In the first study 22 patients (median age 69 (range 60–73) years, 16 men, five diabetic, median resting ABPI 0·57 (range 0·1–0·64)) had their CD and MWD measured on a treadmill set at 3·2 km h^{-1} and 10 per cent gradient. They were then randomized to either GTN or placebo spray, and the distances were remeasured. The crossover portion of the study was then completed. In the second study 28 patients (median age 68 (range 45–84) years, 20 men, six diabetic, median resting ABPI 0·57 (range 0·13–0·98)) were randomized to either GTN or placebo and walked at their own pace along a flat corridor for 15 min. Following a rest of 15 min, the crossover portion of the study was completed. Statistical analysis was by the Wilcoxon matched pairs signed rank test.

Results:

	Placebo	GTN	*P*
Study 1			
CD (m)	70	70	0·59
MWD (m)	105	125	0·008
Study 2			
MWD (m)	825	900	0·02

Conclusion: GTN can increase the MWD by 19 per cent when patients with intermittent claudication are walked on a treadmill and by 9 per cent when walking at their own pace on a flat gradient.

Analysis of cold provocation thermography in the objective diagnosis of the hand–arm vibration syndrome

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Background: The hand–arm vibration syndrome (HAVS) is the commonest prescribed disease in the UK. Presently the diagnosis is subjective and the need for an objective investigation to support the diagnosis has been highlighted. This study analyses the potential of cold provocation thermography (CPT) to fulfil this role.

Methods: CPT was performed in ten controls (five men, five women; median age 35 (range 24–78) years) and 21 patients with HAVS (20 men, one woman; median age 45 (range 29–81) years). With an infrared camera, a precooling (PC) image was taken and then, following hand cooling in water at a temperature of 5°C for 1 min, further rewarming images were taken every minute for 10 min.

Results: Patient finger tip temperatures were significantly cooler than control temperatures at all time points ($P < 0{\cdot}01$, Student's t test). The following *Table* shows the sensitivity, specificity and PPV of CPT.

Rewarming time (min)	Sensitivity (%)	Specificity (%)	PPV (%)
PC	67	88	93
0	24	100	100
1	24	100	100
2	24	100	100
3	95	88	95
4	95	88	95
5	90	88	95
6	95	88	95
7	100	75	91
8	100	88	95
9	90	88	95
10	86	75	90

PPV, positive predictive value

Conclusion: CPT provides strong objective evidence to support the clinical diagnosis of HAVS.

In situ replacement of infected aortic grafts with rifampicin-bonded prostheses

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Background: Prosthetic graft infection following abdominal aortic aneurysm (AAA) surgery is life threatening. Treatment options include total graft excision and extra-anatomic bypass or *in situ* replacement of the graft. The latter option is gaining popularity but the long-term outcome remains uncertain, particularly in light of the increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) infection. A retrospective study was undertaken to assess the outcome after graft excision and *in situ* replacement with a rifampicin-bonded prosthesis for the treatment of major aortic graft infection. The prevalence of MRSA and its influence on outcome was also assessed.

Methods: Over 6 years between January 1992 and December 1997, 11 patients (eight men) with major aortic graft infection underwent total graft excision and *in situ* replacement with a rifampicin-bonded prosthesis.

Results: The median age was 66 (range 49–78) years. Four patients presented with haemorrhage from an aortoenteric fistula, three had retroperitoneal abscess, two had graft occlusion, one had a perigraft collection on computed tomography and one presented with a ruptured suprarenal false aneurysm. Organisms were cultured from ten patients. *Staphylococcus epidermidis* and *Streptococcus faecalis* were predominant. MRSA was isolated from two patients, both of whom had originally undergone ruptured AAA repair. Two patients died and three suffered non-fatal complications. Two patients died during follow-up, one from suspected ongoing MRSA infection and the other from recurrent graft infection. Seven patients remain alive and clinically free from infection, although two were lost to follow-up at 12 and 15 months.

Conclusion: The long-term results following total graft excision and *in situ* replacement with a rifampicin-bonded prosthesis appear to be favourable. MRSA infection seems to be associated with a poor prognosis.

Inhibition of systemic fibrinolysis is associated with myocardial injury in patients operated on for ruptured abdominal aortic aneurysm

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Background: Previous work has demonstrated that ruptured abdominal aortic aneurysm (AAA) is associated with systemic thrombin generation and inhibition of systemic fibrinolysis. The procoagulant and hypofibrinolytic state associated with ruptured AAA predisposes to microvascular and macrovascular thrombosis and subsequent myocardial injury. The aim of this study was to determine the relationship between haemostatic derangement and biochemical evidence of myocardial injury in patients operated on for ruptured AAA.

Methods: Ten patients undergoing repair of ruptured AAA were studied. Tissue plasminogen activator (tPA) activity, plasminogen activator inhibitor (PAI) activity, prothrombin fragment (PF) 1 + 2, D-dimer and fibrinogen levels were measured before operation, and immediately before and 5 min after aortic clamp release. Plasma levels of cardiac troponin (cTn) I were measured before operation, and 6 and 24 h after aortic clamp release.

Results: There was no relationship between tPA activity, PF 1 + 2, D-dimer or fibrinogen and cTn-I levels at any sampling point. There was, however, a significant positive correlation (Spearman rank test) between PAI activity immediately before (median 38·6 (range 13·0–39·4) units ml^{-1}) and 5 min after (37·2 (10·6–39·4) units ml^{-1}) aortic clamp release, and cTn-I at 6 h (median 3·17 (range less than 0·5 to 71·1) ng ml^{-1}) and 24 h (5·55 (range less than 0·5 to 110) ng ml^{-1}) after aortic clamp release.

PAI activity	cTn-I	r	P
Immediately before	6 h after	0·829	0·042
Immediately before	24 h after	0·762	0·028
5 min after	6 h after	0·943	0·005
5 min after	24 h after	0·881	0·004

All sampling points relate to aortic clamp release

Conclusion: These data strongly support the hypothesis that the inhibition of systemic fibrinolysis which occurs in response to ischaemia and reperfusion during ruptured AAA repair contributes to the development of subsequent myocardial injury.

Total abdominal approach for repair of type IV thoracoabdominal aortic aneurysm

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Background: The total transabdominal approach for thoracoabdominal aneurysm (TAA) was described in 1995 and it was suggested that outcome might be improved if the chest was not opened This study reports early results of the technique with respect to operative morbidity and mortality rates for patients with abdominal aortic aneurysm extending to the diaphragm.
Methods: Between 1995 and 1998, 26 patients (median age 71 (range 52–84) years) underwent repair of a type IV TAA using a total abdominal approach and medial visceral rotation.
Results: Three patients presented with a contained leak. All survived but one developed paraplegia. Other complications included chest infection (five patients), myocardial infarction (three), reoperation for bleeding (three) and temporary dialysis in one patient. There were three perioperative deaths, two from myocardial infarction and one from multisystem organ failure.
Conclusion: The total abdominal approach for the repair of type IV TAA is a reasonable alternative to a full thoracoabdominal incision. Thoracic complications are minimized, renal and visceral ischaemia times are low, and the perioperative mortality rate is acceptable.

Long-term survival following repair of ruptured abdominal aortic aneurysm in patients over 75 years of age

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Background: Previous studies have indicated that patients over the age of 75 years have an increased in-hospital mortality rate following repair of ruptured abdominal aortic aneurysm (AAA). The long-term survival of this patient group has not been reported previously, even though this information may have a strong influence on the decision to operate.
Methods: Interrogation of a prospective database identified 272 patients aged 75 years or over (median age 78 (range 75–93) years) admitted between 1983 and 1995. Long-term patient survival data and survival curves for an age- and sex-matched population were obtained from the General Register Office through the Information and Statistics Division.
Results: Sixty-nine (25 per cent) of the 272 patients did not undergo operation. Eighty-eight (43 per cent) of the 203 patients who had surgery died within the same hospital admission. The 1-, 5- and 10-year survival rates for the remaining 115 patients (median age 77 (range 75–85) years) were 88, 59 and 26 per cent respectively, at a median follow-up of 54 (range 1–157) months. The median life expectancy for this patient group was 69 months. These data are comparable to those of an age- and sex-matched population.
Conclusion: Many patients over the age of 75 years who present with ruptured AAA are considered unfit for surgery. These data demonstrate that, even in this elderly population, survivors of ruptured AAA repair enjoy a near-normal life expectancy.

Perioperative renal function following endovascular repair of abdominal aortic aneurysm with suprarenal and infrarenal stents

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Background: Endovascular repair (EVR) of abdominal aortic aneurysm (AAA) is feasible for selected patients. Placing an uncovered stent across the origins of the renal arteries may improve fixation and seal of the proximal end of the stent-graft. However, this has potential for problems (e.g. renal artery stenosis or microembolization). This study aimed to evaluate the short-term effect of a suprarenal stent on the function of the individual kidney
Methods: In 30 patients undergoing EVR for AAA, renal function was assessed before and after operation by ^{99m}Tc-radiolabelled diethylenetriamine penta-acetate radionuclide renography and daily measurement of serum creatinine levels. Eleven patients had infrarenal stent-grafts using an aorta uni-iliac system (group 1); 19 patients had the device with an uncovered suprarenal stent (modified Gianturco Z stent), ten of which were aorta uni-iliac and nine bifurcated systems (group 2). Individual kidney function was expressed as the whole kidney transit time (WKTT). In addition, glomerular filtration rate (GFR) was measured from serial blood samples following renography.
Results:

	Group 1 ($n = 11$)		Group 2 ($n = 19$)	
WKTT (min)*				
Preop.	R 6·8(0·9)	L 6·5(1·0)	R 5·7 (0·6)	L 5·7(0·5)
Postop.	R 6·4(0·8)	L 6·9(1·0)	R 5·5(0·4)	L 5·5(0·5)
GFR (ml min^{-1})*				
Preop.	64(6)		53(6)	
Postop	71(7)		54(8)	
Maximum creatinine rise (µmol ml^{-1})†	5 (0–53)		12 (0–423)	
Mean contrast volume (ml)	244		297	

*Values are mean(s.d.), †values in parentheses are ranges

Conclusion: No result reached statistical significance. Placing an uncovered stent over the origins of the renal arteries does not appear to impair kidney function in the short term.

Changes in proximal aortic neck dimensions following endovascular repair of abdominal aortic aneurysm

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Background: Dilatation of the proximal neck following conventional open repair of abdominal aortic aneurysm (AAA) has been reported. Such continued dilatation following endovascular repair (EVR) could potentially be a disaster resulting in graft slippage, endoleak and aneurysm rupture. The aim of this study was to detect any change in proximal neck diameter following EVR of AAAs.

Methods: One hundred patients had undergone EVR of an AAA over a 4-year period in whom contrast-enhanced spiral computed tomography was performed both before and after EVR (1 week, 3, 6 and 12 months and annually thereafter). Change in aortic proximal neck diameter, change in maximum aortic diameter, presence of endoleaks, and change in length from the lowest renal artery to the aortic bifurcation was sought.

Results: The median anteroposterior and transverse diameter decreased from 64 mm before operation to 56 and 54 mm respectively after operation. This trend in reduction in maximum diameter was not seen in patients with endoleaks. There was no significant change in proximal neck diameter when measured at 5-mm intervals following EVR. There was also no significant change in the aortic length following EVR.

Conclusion: There was no evidence of proximal neck dilatation or aneurysm length reduction following EVR of AAAs.

Prevention of lumbar artery endoleaks following endovascular abdominal aortic aneurysm repair with the selective use of absorbable gelatin sponge

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Background: The aim of endovascular repair of an abdominal aortic aneurysm is to exclude the aneurysm from the systemic circulation in order to prevent aneurysm expansion and rupture. Lumbar artery (LA) endoleaks have been associated with continued expansion of the aneurysm sac and occur with a reported incidence of approximately 10 per cent. The aim of this study was to reduce the incidence of LA or inferior mesenteric artery (IMA) endoleaks.

Methods: Following deployment of an aortic uni-iliac graft an aneurysmograph was performed by injecting contrast into the aneurysm sac to look for patent aortic side branches. Patients with no visible side branches had an occluder deployed in the contralateral iliac artery. Patients with patent side branches had an absorbable gelatin sponge inserted into the aneurysm sac before occluder deployment. Patients had contrast-enhanced spiral computed tomography (CT) during follow-up at 1 week, and 3, 6 and 12 months.

Results: Fifty-four patients were studied. Eleven were excluded (two perioperative deaths, seven top endoleaks and two occluder endoleaks). Median follow-up was 2 (range 11–7) months. Of the 17 patients in whom patent vessels were demonstrated on an aneurysmograph, one had a patent IMA only, three had a patent LA and IMA, and the remainder had a patent LA. No patient within the study has had a LA or IMA endoleak identified at follow-up CT.

Conclusion: An intraoperative aneurysmograph can help select patients for aneurysm sac packing with gelatin sponge and has been successful in the short term in preventing LA and IMA endoleaks.

Endovascular aortic aneurysm repair reduces mortality: a physiological analysis

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Background: Endovascular techniques are gaining acceptance as minimally invasive methods for abdominal aortic aneurysm repair, although there have been few studies that provide direct comparison with conventional techniques. A prospective study that compares morbidity and mortality rates following abdominal aortic aneurysm repair, using a physiological scoring system, is presented.

Methods: Between December 1994 and November 1997, 104 elective open aneurysm repairs and 49 endovascular aneurysm repairs were performed at this institution. These patient cohorts were compared using the Portsmouth predictor equation scoring system, which has been shown to predict outcome in vascular surgery. Prospective data from patient notes were used to obtain physiological and operative severity scores that were analysed to predict expected (E) to observed (O) mortality and morbidity rates.

Results:

	Endovascular ($n = 49$)	Conventional ($n = 104$)
Mortality*		
O	3 (6)	17 (16)
E	4·0 (8)	19·8 (19)
O : E ratio	0·75	0·86
Morbidity*		
O	21 (43)	75 (72)
E	11·9 (24)	48·4 (47)
O : E ratio	1·76	1·55
Physiological score†	20·8(5·6)	20·1(5·0)
Operative severity†	19·7(1·7)	26·3(2·1)

*Values in parentheses are percentages. †Values are mean(s.d.)

Although physiological variables were equivalent in both groups, conventional surgery had a higher mortality ($P < 0.05$) and morbidity ($P < 0.001$) rate than endovascular surgery, which was related to the operative severity scores.

Conclusion: These data suggest that open aortic aneurysm repair has a higher operative severity than endovascular repair which may be reflected in increased mortality rates.

Immunoglobulin A antibodies against *Chlamydia pneumoniae* are associated with expansion of small abdominal aortic aneurysms and declining ankle blood pressure

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Background: The potential correlation between chronic infection with *Chlamydia pneumoniae* and the progression of small abdominal aortic aneurysms (AAAs) and lower limb atherosclerosis was studied.

Methods: Mass screening for AAA was carried out in outdoor clinics at all hospitals in the county. Some 139 men (aged 65–73 years) with a 3·0–4·9-cm AAA were followed prospectively for 1–3 (mean 2·7) years. Initially, an interview and examination was performed, and blood samples were taken.

Results: Some 62 per cent (53–71 per cent) had an immunoglobulin (Ig) A level of 40 or more, or an IgG level of 64 or above. Some 83 per cent (74–93 per cent) had an IgA level of 20 or more, or an IgG level of 32 or more. Men with an IgA level of 20 or more had 51 per cent greater AAA expansion and men with an IgA level of 40 or above had 24 per cent more expansion. An IgA level of 20 or more, or IgA of 40 or greater, were significant independent predictors of AAA expansion adjusted for age, smoking, initial AAA size, steroid treatment, diastolic blood pressure, pulmonary function and other plasma factors. The ankle blood pressure index (ABI) of the IgA-seropositive men decreased 11 per cent, while the ABI decreased by 5 per cent among IgA-seronegative men ($P < 0.05$). The significant difference persisted after adjusting for age, smoking, initial systolic ankle blood pressure, initial brachial systolic or diastolic blood pressure, but disappeared after adjusting for low-density lipoprotein (LDL) levels.

Conclusion: A high proportion of men with a small AAA have signs of chronic *C. pneumoniae* infection. The progression of AAAs and lower limb atherosclerosis seems to be correlated to chronic infection with C. *pneumoniae.*

Autologous transfusion reduces blood transfusion requirements in aortic surgery

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Background: Elective aortic surgery is associated with a blood loss that warrants a routine blood crossmatch of 4–6 units. Autologous transfusion strategies to reduce blood requirements were evaluated in a pilot study involving six hospitals in the North West.

Methods: Eighty patients undergoing elective aortic surgery were randomized to either autologous (a combination of acute normovolaemic haemodilution and intraoperative cell salvage) or homologous transfusion. The transfusion trigger, in the absence of pressing clinical need, was 8 g dl^{-1} haemoglobin for both groups.

Results: Randomization achieved two groups well matched for age, aneurysm or occlusive surgery, aspirin intake, estimated blood volume, preoperative haemoglobin and aneurysm size. In the 'best' hospitals ($n = 49$) mean(s.d.) blood loss (630(49) ml) was significantly lower ($P < 0.01$) than that in the 'worst' hospitals (1077(110) ml, $n = 31$) and fewer patients required transfusion (nine of 42 *versus* 15 of 30; $P < 0.05$). No significant differences were found between homologous and autologous groups for all variables measured in the 'best' hospitals. In the 'worst' hospitals blood requirements were significantly higher ($P < 0.05$) for the homologous group (800(112) ml) compared with the autologous group (489(65) ml), although blood loss was similar (1239(195) *versus* 915(92) ml respectively).

Conclusion: Autologous transfusion techniques significantly reduced homologous blood requirements in aortic surgery where blood loss exceeded 800 ml.

Randomized double-blind study of dopexamine *versus* placebo in aortic surgery

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Background: Mechanisms involved in the development of colonic ischaemia are not fully understood and there are conflicting reports regarding predisposing factors. The aim of this study was to evaluate the effect of dopexamine hydrochloride on the incidence of colonic ischaemia following aortic surgery and to correlate immunohistochemical markers of inflammatory activation in its pathogenesis.

Methods: Thirty patients, of mean age 65 (range 46–84) years, undergoing elective infrarenal aortic surgery were randomized to receive a perioperative infusion of either dopexamine 2 μg kg^{-1} min^{-1} ($n = 12$) or 0·9 per cent saline placebo ($n = 18$). All patients underwent colonoscopy and biopsy following induction of anaesthesia and at 1 week after operation. Sections were stained with haematoxylin and eosin, and for mast cell tryptase (MCT), myeloperoxidase (MPO) and both the inducible (iNOS) and endothelial (eNOS) isoforms of nitric oxide synthase. Sections were analysed blindly and independently by two histopathologists. Patient and operative data were collected and stored separately.

Results: Colonic ischaemia was noted in nine patients based on microscopic findings. Endoscopy alone had a sensitivity of 56 per cent. There was a significantly lower incidence of colonic ischaemia in patients receiving dopexamine compared with placebo ($P < 0.05$). One death resulted from colonic infarction in the placebo group 11 days after operation. There was increased MPO and MCT expression in patients with histological evidence of ischaemia ($P < 0.05$); iNOS staining within the vascular ($P = 0.001$) and lamina propria ($P < 0.05$) components of the mucosa was also significantly greater. No association was found with eNOS.

Conclusion: Perioperative dopexamine infusion confers a degree of protection to colonic mucosa following aortic surgery, possibly through an anti-inflammatory effect.

Management of coexisting intra-abdominal disease in aortic surgery

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Background: The management of coexisting intra-abdominal disease in aortic surgery is controversial. A staged repair is preferred by many and, in general, the symptomatic lesion is treated first. Twenty-one years ago this vascular unit elected a policy of treating such lesions synchronously. This was on the theoretical premises that the benefits of a single operation in these patients would outweigh the potential risks of graft infection and increased complication rates from a prolonged procedure.

Methods: The case records of 676 patients undergoing aortic grafting for aneurysmal or occlusive disease between 1978 and 1998 were analysed retrospectively.

Results: Fifty-five patients (8 per cent) had coexisting intra-abdominal diseases treated at the time of aortic graft surgery. These included biliary disease (26), and gastric (12), intestinal (13), urological (two), hepatic (one) and splenic (one) pathology. The median age at presentation was 72 (range 46–90) years. There were three hospital deaths and five patients required early reoperation, three for lower limb ischaemia and two for intra-abdominal bleeding. One patient developed a subphrenic abscess and there were three superficial wound infections. There were no graft infections in this group of 55 patients.

Conclusion: This large single-centre experience with synchronous intra-abdominal surgery and aortic grafting demonstrates that it is safe and does not predispose to an increased risk of graft infection or perioperative haemorrhage.

First year of a fast-track carotid duplex service

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Background: The risk of a major stroke after a transient ischaemic attack (TIA) is highest in the first 3 months after the onset of symptoms. Urgent endarterectomy in appropriate cases is recommended through a fast-track one-stop assessment clinic.

Methods: Local general practitioners (GPs) were informed that a duplex scan would be guaranteed within 14 days of referral of any patient who had a recent clearly documented TIA or amaurosis fugax. Referral letters were faxed and the scan was authorized by a consultant surgeon. Those with significant disease were seen in the clinic in preparation for operation. Non-significant results were conveyed by post to the GPs with no further action.

Results: In the first 12 months of the service, 90 scans were performed through the fast track. In the same interval 490 non-fast-track scans were done after request by a physician (38 per cent), geriatrician (24 per cent), neurologist (14 per cent), vascular surgeon (11 per cent), ophthalmologist (8 per cent) or others (4 per cent). Thirteen (14 per cent) of 90 patients in the fast-track group had carotid endarterectomy, with a median period between referral and operation of 30 (range 20–45) days and median time between onset of symptoms and surgery of 7 (range 4–58) weeks. Endarterectomy was carried out in 12 (2 per cent) of 490 patients in the routine group with a median duration between referral and operation of 127 (range 64–184) days.

Conclusion: A fast-track service can significantly reduce the time between referral and operation, and increase the number of endarterectomies. Urgent and appropriate referral from the GPs is vital for the service to work efficiently.

Influence of contralateral stenosis on long-term mortality rate following carotid surgery

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Background: Recent evidence suggests that high-grade contralateral stenosis has an adverse effect on perioperative morbidity in carotid endarterectomy (CEA). The relationship between contralateral high-grade stenosis and long-term survival after CEA was examined.

Methods: Three hundred and twenty-seven patients undergoing 333 CEA operations were entered prospectively into a database and long-term follow-up was instituted. Cardiac and stroke risk factors were identified before operation and correlated with long-term survival and cause of death.

Results: Mean age at operation was 68 (range 42–86) years. Median follow-up was 2 (range 1–8) years. There were 45 deaths (seven perioperative), 17 myocardial, 16 from stroke (four perioperative), five from neoplasia, three respiratory and four others. The cumulative 5-year survival rate was 75 per cent. Patients with high-grade contralateral stenosis (greater than 80 per cent) had a significantly reduced life expectancy after CEA ($P < 0{\cdot}05$).

Conclusion: Severe contralateral carotid disease is not only an adverse perioperative risk factor but also has negative implications for survival of the patient in the longer term. Following CEA, patients in general have a lower life expectancy than a normal age-matched population.

Systemic effects of exercise in claudicants are associated with neutrophil activation

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Background: Claudication induces potentially harmful systemic effects which may be mediated through free radicals and neutrophil activation. This study examined the impact of these mechanisms on renal tubular function.

Methods: Flow cytometry was used to determine CD11b expression by neutrophils and monocytes, and expression of P selectin (CD62P) by platelets, in 16 patients with intermittent claudication and eight matched controls before and at intervals after exercise. Total antioxidant capacity (TAC) and von Willebrand factor (vWF) were measured at similar intervals. Renal

	Before exercise	Time after exercise (min) 0	10	20	30	60
Neutrophils*†						
Patients	79·8(13·6)	87·3(10·7)	88·8(10·9)	84·2(11·6)	89·8(13·6)	85·6(11·7)
Controls	65·1(18·1)	73·7(16·0)	75·9(18·5)	81·6(16·8)	79·4(21·3)	85·7(24·9)
TAC‡						
Patients	1·31(0·14)	1·34(0·18)	1·42(0·17)	1·38(0·16)	1·39(0·17)	1·36(0·17)
Controls	1·30(0·11)	1·34(0·10)	1·30(0·11)	1·33(0·11)	1·32(0·10)	1·34(0·13)

Values are mean(s.d.) *Median expression of monoclonal antibody (per cent gated) †$P = 0·03$, ‡$P \leq 0·01$ (repeated measures analysis of variance) TAC, total antioxidant capacity

tubular function was assessed before and 60 min after exercise by assay of retinol binding protein : creatinine ratio (RBP : Cr) in urine. All patients and none of the controls had a significant exercise-induced fall in ankle pressure. Fluorescein isothiocyanate-labelled monoclonal antibodies against CD11b and CD62P were added to blood and analysis was performed on the flow cytometer within 72 h.

Results: There were no significant differences in monocytes, platelets or vWF between patients and controls over time. There was a significant change in RBP · Cr following exercise in patients (median 4·2 (95 per cent confidence interval 2·4–85·2); $P \leq 0·01$, Wilcoxon test) but not controls (2·7 (–1 to 7·5), P not significant). See *Table* above.

Conclusion: Renal tubular function was adversely affected by acute exercise in claudicants. TAC was higher in claudicants at rest and was increased after exercise suggesting an increased free radical challenge. Neutrophil activation is significantly different between claudicants and controls before and after exercise, and may provide a link between free radical generation and renal tubular injury.

Outcome after ligation of infected false femoral aneurysms in intravenous drug abusers

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Background: Infected false femoral aneurysm (IFFA) is a life-threatening complication of intravenous drug abuse and presents a difficult management problem for the vascular surgeon. Controversy exists regarding the best management. The choice lies between ligation and excision with immediate revascularization, and ligation and excision with observation; reconstruction is reserved for critical ischaemia.

Methods: After disappointing results with the former method it was decided to perform ligation and excision with observation as the initial treatment of IFFA. A 9-year experience of 28 patients treated at this hospital is reviewed.

Results: In 26 cases of primary ligation and excision of an IFFA there were no amputations and patients described claudication only in follow-up. In two cases of a second IFFA in the same limb, repeat ligation and excision resulted in one viable limb with claudication only and one above-knee amputation for non-viability. At 9-year follow-up (80 per cent complete), over 90 per cent of the patients were still drug abusers and therefore not suitable for revascularization. There were two deaths, both of which were drug related.

Conclusion: Ligation and excision of an IFFA is simple, effective and safe, and is the most appropriate method of dealing with these challenging patients.

Symptoms of varicose veins

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Background: The relationships between varicose veins (VVs) and leg symptoms have not been studied. The aim of this study was to define the relationships between age, sex, leg symptoms and VVs.

Methods: An age-stratified sample of 699 men and 867 women aged 18–64 years, selected randomly from 12 general practices distributed socioeconomically throughout the city, completed a questionnaire regarding leg symptoms (heaviness/tension, swelling, aching, restless legs, cramps, itching, tingling) and underwent a clinical examination.

Results: In men, swelling and cramps (both $P \leq 0·001$), and in women swelling ($P = 0·02$), restless legs ($P = 0·001$) and itching ($P = 0·045$), were significantly more common in older subjects. Data have therefore been age adjusted. Women were significantly ($P < 0·01$) more likely to respond positively when asked about all leg symptoms, except tingling. The commonest symptoms were aching in women (53·8 per cent) and cramps in men (34·0 per cent). There was no difference between right and left legs. In men, only itching was significantly related to trunk VVs ($P = 0·011$). In women, there was a relationship between trunk VVs and heaviness/tension, aching and itching ($P \leq 0·005$). Hyphen-web varices were not related to symptoms in men but were related to heaviness/tension and swelling in women. There was no association between reticular varices and symptoms in either sex.

Conclusion: Even in the presence of VVs, most lower limb 'venous' symptoms are non-venous in aetiology. Surgery is unlikely to ameliorate symptoms in the majority of patients.

Mid-term results of arterial allograft below-knee bypasses for limb salvage

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Background: Arterial allografts (AAs) have been recently reconsidered in the treatment of critical limb ischaemia when vein material is absent, because of the disappointing results with artificial grafts. The aim of this study was to report the results observed in three centres where AAs were used for infrainguinal reconstruction in critical limb ischaemia.
Methods: Between 1991 and 1997, 165 AA bypasses were performed in 148 patients (90 men) with a mean age of 70 (range 20–93) years. Indications for operation were rest pain in 54 patients and tissue loss in 111. Mean resting ankle pressure was 53 mmHg in 96 non-diabetic patients and mean transcutaneous partial pressure of oxygen was 10 mmHg in 52 diabetic patients. AAs were obtained from cadaveric donors. The distal anastomosis was to the below-knee popliteal artery in 34 cases, to a tibial artery in 114 and to a pedal artery in 17.
Results: At 30 days, the mortality rate was 3 per cent, primary patency 83 per cent, secondary patency 90 per cent and limb salvage rate 98 per cent. During follow-up (mean 31 months) 65 grafts failed primarily. Causes of primary failure were thought to be progression of the distal disease in 15 cases, myointimal hyperplasia in 16, graft degradation in ten (four dilatations, three stenoses, two ruptures and one dissection), other causes in eight and not known in 16. Primary and secondary patency rates at 3 years were 35(s.e. 9) per cent and 42(s.e. 10) per cent. The limb salvage rate at 3 years was 76(s.e. 8) per cent.
Conclusion: AAs lead to a good foot salvage rate but poor patency rates. The results are similar to those obtained with polytetrafluoroethylene grafts.

New technique of *in situ* autogenous venous valve construction using varicose vein and bench hydrostatic testing of its properties *in vitro*

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Background: Long-term results of valve transposition and autogenous valve grafts (from axillary and brachial vein) for chronic venous insufficiency due to post-thrombotic valve destruction are poor. Attempts at constructing *in situ* autogenous venous valves using varicose veins have been ongoing since 1953 but have been unsuccessful. A technique has been developed to create new autogenous *in situ* valve.
Methods: Varicose long saphenous veins were obtained following stripping during routine varicose vein surgery. A longitudinal elliptical segment of vein wall was excised from opposite sides; this effectively reduces the diameter of the vein. Polypropylene sutures were applied on each side, starting at the centre of the elliptical defect, and brought out proximally. After closing the elliptical defects, gentle traction was applied to the initial sutures and they were tied causing invagination of the vein wall. Both ends of the vein were connected to pressure transducers and a standard pressure monitoring device. Normal saline was pumped at various pressures through the valve-bearing segment while pressures were recorded simultaneously.
Results: Fourteen constructed valves were tested for their bench hydrostatic properties. Mean(s.d.) minimum opening pressure of the valves was 5·3(2·4) mmHg. The valves were competent at a minimum pressure of 2·7(0·6) mmHg. They sustained sudden pressures of up to 139·0(13·8) mmHg and remained competent at a maximum pressure of 260 mmHg.
Conclusion: This technique produces a competent one-way valve capable of sustaining high back pressures, while allowing forward flow with minimal resistance.

Randomized controlled trial of heparin plus graduated compression stocking for the prophylaxis of deep venous thrombosis in general surgical patients

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Background: A randomized controlled study was undertaken to compare heparin with heparin plus graduated compression stockings (Brevet Tx, Seton Healthcare) in the prophylaxis of deep vein thrombosis (DVT) following abdominal surgery.
Methods: Sixty high-risk patients were recruited if they met at least two of the following criteria identified as predisposing to DVT. age greater than 39 years, malignancy, varicose veins, cardiac disease or hypertension, diabetes mellitus, obesity or previous thromboembolic episode. All patients received subcutaneous heparin and were randomized to receive Brevet Tx to either the right or left leg before surgery. The stocking was worn for 2 weeks after surgery. The patients underwent duplex imaging before surgery, and at 3, 6 and 14 days after operation. All scans were performed by one sonographer. The policy was to perform a venogram where a positive result was indicated by duplex scanning.
Results: Fifty-six patients completed the study. Six patients (11 per cent) suffered a DVT in the non-stockinged leg, but none in the stockinged leg ($P = 0·016$, McNemar's test). The DVTs occurred on days 3, 6, 7, 8, 9 and 12 following surgery.
Conclusion: Brevet Tx in addition to low-dose subcutaneous heparin significantly reduced the incidence of DVT in high-risk patients undergoing abdominal surgery.

Role of superficial vein surgery in treatment of venous ulceration

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Background: Recent colour duplex studies of patients presenting with venous ulceration in the community have shown that between 55 and 60 per cent have isolated superficial venous insufficiency. Previous studies of the role of superficial surgery in the treatment of venous ulceration have applied postoperative compression bandaging and therefore it has not been possible to determine the role of superficial surgery in promoting ulcer healing. The purpose of this prospective study was, therefore, to examine the healing rate after superficial surgery in patients with isolated superficial venous incompetence and venous ulceration who did not undergo postoperative compression bandaging.

Methods: Patients with isolated superficial venous incompetence, as demonstrated by colour duplex scanning and an ankle brachial pressure index greater than 0·8, underwent saphenofemoral or saphenopopliteal disconnection under local anaesthesia, or a high tie and strip under general anaesthesia. Compression bandaging was not applied after operation. Patients were followed regularly after surgery and the endpoint was ulcer healing.

Results: Between May 1994 and July 1997, 122 legs with venous ulceration and isolated superficial venous incompetence underwent superficial surgery. Ninety-three (76 per cent) had long saphenous incompetence alone, 13 (11 per cent) had short saphenous incompetence alone and 16 (13 per cent) had combined long and short saphenous incompetence. The median (range) patient age was 72 (28–94) years and the median duration of ulceration was 32 weeks (range 2 weeks to 32 years). The median (range) ulcer area was 9 (1–500) cm^2. Ninety patients (74 per cent) had a local anaesthetic procedure while 32 (26 per cent) had general anaesthesia. Of patients who had long saphenous surgery, 69 had high ligation only and 24 had high ligation and strip. The healing rate by life-table analysis was 58 per cent at 6 months, 73 per cent at 1 year and 82 per cent at 18 months. Clinical review and colour duplex examination of patients with ulcers that had failed to heal ($n = 18$) showed that two had recurrent superficial to deep connections; the remainder had fixed ankle joints or severe osteoarthritis of the hip and knee.

Conclusion: Superficial venous surgery in patients with isolated superficial venous incompetence and venous ulceration can achieve a very high healing rate in the absence of postoperative compression.

Contribution of malnutrition to postoperative morbidity in vascular surgical patients

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Background: In an elderly population of surgical patients, poor mobility, poor diet and chronic disease contribute to a significant risk of malnutrition. Malnutrition is associated with muscle weakness, fatigue, poor wound healing and immunological dysfunction. The aim of the study was to establish the prevalence of malnutrition in vascular surgical patients and to compare postoperative infection rates in well nourished and malnourished patients.

Methods: A nutritional assessment was performed on 71 patients (49 men; median age 65 (range 26–85) years) attending pre-assessment for vascular surgical procedures. Nutritional status was measured using validated indicators of malnutrition. estimated weight changes over 3 months; body mass index; mid-arm muscle circumference (MAMC) calculated using triceps skin fold thickness (TSF) and mid-arm circumference (MAC) (MAMC = MAC – (3·14 × TSF)); and serum albumin concentration. Fifty-nine patients were followed after vascular surgery. The incidence of postoperative infections was related to preoperative nutritional status.

Results: Nineteen patients (27 per cent) had normal values for all nutritional indicators examined. The remaining 52 patients (73 per cent) had one (37), two (12), three (two) or four (one) nutritional indicators within the range for malnutrition. Among the 59 patients who underwent surgery there were five chest infections, seven wound infections, one urinary tract infection and one infected central line in 13 patients following six femorodistal bypasses, four abdominal aortic aneurysm repairs and three miscellaneous arterial procedures. The incidence of septic complications was zero in 14 patients with normal nutritional indicators and 41 per cent (13 of 32) in patients with indicators of malnutrition ($P < 0·05$, Fisher's exact test).

Conclusion: Malnutrition is prevalent among vascular patients and may contribute to postoperative morbidity. Malnourished patients should be identified and referred to the dietician at the earliest opportunity to minimize the morbid effects of undernutrition.

Prevalence and significance of thrombophilia in patients with intermittent claudication

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Background: Thrombophilia may be associated with premature atherosclerosis, an increased susceptibility to primary arterial thrombosis and an increased failure rate for peripheral vascular or endovascular interventions. The aim of this study was to determine the prevalence of thrombophilia in patients with intermittent claudication (IC).

Methods: This was a prospective study of 116 consecutive new patients (70 men; median age 65 (range 43–84) years) referred to this regional vascular surgery unit with IC. Patients on warfarin, or who had previously undergone lower limb reconstruction and/or angioplasty, were excluded.

Results: Thrombophilia was demonstrated in 24 patients (21 per cent). The commonest abnormality (15 patients, 13 per cent) was a raised level of anticardiolipin antibody (ACLA) (11 immunoglobulin (Ig) M, four IgG). Other abnormalities comprised. lupus anticoagulant (one), protein C deficiency (two), protein S deficiency (two), activated protein C resistance (one) and factor V Leiden heterozygosity (three). All abnormalities were confirmed on repeat testing. No patient had a history of venous thrombosis. There was no statistically significant relationship between ACLA status and age, sex, ankle : brachial pressure index, previous myocardial infarction or stroke, previous carotid endarterectomy or coronary artery surgery, serum cholesterol, current use of antiplatelet agents or current smoking status.

Conclusion: Almost one-quarter of new patients referred to this regional vascular unit with IC have thrombophilia, over half of those affected have a raised ACLA level compatible with the antiphospholipid syndrome. At present, the clinical significance and management implications of these abnormalities remain unknown.

Integrated care pathways for vascular surgery

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Background: Integrated care pathways (ICPs) represent a multidisciplinary approach to clinical patient care.

Methods: A 1-year prospective trial of the use of ICPs for elective vascular surgical procedures was undertaken. A multidisciplinary group constructed ICPs for patients admitted for open repair of abdominal aortic aneurysm, carotid endarterectomy or femoropopliteal bypass grafting. Patient management followed ICPs on a daily basis with signatures required to confirm that each action had been taken. Variances from the ICPs were carefully recorded. Audit of variance data allowed subsequent revision of the ICPs and hence provision of the best possible nursing and clinical practice.

Methods: A total of 33 patients were entered into the study; 16 had a femoropopliteal bypass graft, eight carotid endarterectomy and nine open repair of an abdominal aortic aneurysm. ICPs were well received by patients and staff. They improved communication, promoted an appreciation of each health group's role in patient care, increased nursing autonomy, reduced calls to junior medical staff, improved patient education and confidence, and caused a marked reduction in length of hospital stay. Overall, patients were discharged 13 per cent earlier after open abdominal aortic aneurysm repair, 22 per cent earlier after carotid endarterectomy and 38 per cent earlier after femoropopliteal bypass grafting.

Conclusion: ICPs have clear benefits. They improve overall clinical efficiency and enhance clinical governance. Successful use of ICPs depends upon 'clinical champions' and effective project management. Sufficient resources and training are essential.

Review of out-of-hours vascular procedures in a tertiary vascular unit

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Background: The aim of this study was to review out-of-hours vascular procedures in a tertiary vascular unit.

Methods: The vascular emergencies that presented outside normal working hours (17.00 to 08.00 hours) in a vascular unit between January and June 1998 were reviewed. Only cases considered to be life or limb threatening and requiring urgent surgical or radiological intervention were assessed.

Results:

1998	Out-of-hours procedures	Tertiary referrals
January	15	11
February	20	12
March	18	10
April	22	10
May	21	12
June	23	13

The *Table* shows that a significant number of vascular emergencies was performed out of hours in one unit. This was, in part, due to an increase in the number of tertiary referrals, which represented 57 per cent of all emergency procedures. Reasons for the tertiary referrals were: no consultant vascular surgeon on call (33 per cent), no consultant interventional radiologist on call (26 per cent), lack of intensive care beds (30 per cent) and complex procedure (11 per cent). The overall mortality rate of patients referred in this period was 15 per cent The unit has three consultant vascular surgeons, two consultant interventional radiologists and one vascular specialist registrar.

Conclusion: The significant increase in out-of-hours vascular emergencies, both surgical and radiological, has placed an enormous demand on senior members of the team. In addition, it has had a significant impact on the unit's elective admissions and waiting lists, in particular those for routine general surgery. To support the growth in complex emergency referrals, senior vascular fellows in both vascular surgery and radiology have been appointed and proposals are underway to restructure local vascular services.

Provision of an emergency vascular service: a three-hospital model

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Background: A new emergency vascular cover service came into effect on 1 May 1997 involving three district general hospitals, eight surgeons and covering a patient population of 600 000. Each week one of the three hospitals is on call, accepting the transfer of patients requiring urgent surgical or radiological vascular intervention between 17.00 and 09.00 hours each weekday and throughout the weekend from the other two hospitals. The aim of this project was to evaluate the pattern, appropriateness of referral and increased workload in the first year following the implementation of this model of emergency vascular cover.

Methods: A retrospective study of case notes was conducted identifying all acute vascular emergency admissions from each hospital.

Results: The total number of emergency admissions when on call was 140; 71 per cent were admitted via bed bureau/accident and emergency, 26 per cent were transfers from the other two hospitals and 3 per cent were transfers from elsewhere. Some 66 per cent of admissions occurred between 17.00 and 09.00 hours or at weekends; 36 per cent required emergency operation. Of these patients, 42 per cent required abdominal aortic aneurysm repair, 42 per cent an embolectomy, 11 per cent an amputation and 5 per cent another procedure. Consultants performed 58 per cent of the emergency operations, specialist registrars 37 per cent and senior house officers 5 per cent. Of the total number of emergencies admitted, 12 per cent required intensive care unit facilities. Some 63 per cent of the patients were finally discharged, 11 per cent were transferred and 25 per cent died.

Conclusion: These data demonstrate that one consultant-led vascular team can provide an out-of-hours emergency vascular service for a population served by three hospitals. The workload is manageable without the predicted drain on resources and is preferred by the participating consultants.

Systematic review of intra-arterial thrombolytic therapy for peripheral vascular occlusions

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Background: A systematic review of intra-arterial thrombolytic therapy for peripheral vascular occlusions was undertaken.

Methods: The four major electronic databases (Medline, Cinhal, Embase and The Cochrane Library) were searched to identify randomized controlled trials of thrombolytic therapy in the treatment of limb ischaemia. The search was limited to English language articles, or those that provided a sufficiently detailed English summary, and to articles published after 1980. Trials were considered for inclusion if they were randomized controlled trials, systematic reviews or meta-analyses. Data were extracted independently by two reviewers and aggregate outcomes were obtained using a random effects meta-analysis.

Results: A total of 32 articles were found but only 12 were assessed to be of sufficient quality to be included in the review. There was a distinct lack of large randomized controlled trials comparing thrombolysis with surgical management. The exceptions were the Thrombolysis or Peripheral Arterial Surgery (TOPAS) and Surgery *versus* Thrombolysis for Ischemia of the Lower Extremity (STILE) trials, but both had some methodological flaws. The STILE trial did not achieve the sample size originally determined and the TOPAS trials had a large number of contributing centres (113) compared with the sample size (548). Meta-analysis showed no significant differences between thrombolysis and surgery in terms of major amputation (relative risk (RR) 0·9 (95 per cent confidence interval 0·6–1·4)) and death (RR 1·2 (0·8–1·9)). However, there was an increased risk of residual ischaemia with thrombolysis (RR 1·8 (1·2–2·5)) and haemorrhage (RR 2·9 (1·1–7·9)). Patients who were shown to benefit from thrombolysis were those with short-duration ischaemia (RR reduction, 72 per cent; numbers needed to treat, three) and occluded grafts (RR reduction, 58 per cent; numbers needed to treat, four).

Conclusion: Despite the theoretical advantages of thrombolysis, there is still insufficient evidence to justify its widespread use except in patients with graft occlusions and short-duration ischaemia.

Percutaneous transluminal angioplasty for lower limb ischaemia

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Background: Percutaneous transluminal angioplasty (PTA) is increasingly performed for lower limb ischaemia of all severities, despite the absence of controlled data demonstrating its efficacy. The aim of this study was to examine the indications and outcome for lower limb ischaemia over a 16-year period.

Methods: A prospectively gathered database of 1287 consecutive PTAs performed between 1982 and 1997 was analysed. Two time intervals were compared· 1982–1991 and 1992–1997.

Results: Since 1992 there has been a fourfold increase in the number of PTAs performed. There has been a significant increase in the number of PTAs performed for critical ischaemia, occlusive lesions and at infrainguinal sites. Although there has been a significant reduction in morbidity, the number of immediate technical and clinical failures has increased (see *Table*).

	1982–1991 (n = 254)	1992–1997 (n = 1033)
Indication*		
Claudication	178 (70)	630 (61)
Critical ischaemia	76 (30)	403 (39)
Disease*		
Stenosis	243 (96)	830 (80)
Occlusion	11 (4)	203 (20)
Site*		
Iliac	183 (72)	502 (49)
Femoral	67 (26)	466 (45)
Popliteal + crural	4 (2)	65 (6)
Major morbidity*	22 (9)	53 (5)
Technical failure	16 (6)	54 (5)
Immediate clinical failure	26 (10)	127 (12)

Values in parentheses are percentages. *χ^2 test with Yates' correction

Conclusion: Despite a lack of controlled data supporting a more liberal use of PTA in the treatment of lower limb ischaemia, there has been, in this regional vascular unit, a significant increase in the perceived clinical and anatomical indications for the procedure. Randomized controlled trials are urgently required to define the role of PTA in this condition.

Outcome of iliac percutaneous transluminal angioplasty with and without the use of stents in patients with intermittent claudication

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Background: Despite the absence of controlled data supporting endovascular treatment of iliac disease in patients with intermittent claudication (IC), there has been a significant increase in iliac percutaneous transluminal angioplasty (PTA), and in particular iliac stenting, in recent years. The clinical and haemodynamic outcome of iliac PTA, with and without stenting, was assessed in patients with IC.

Methods: A prospectively gathered computerized database of iliac PTA ($n = 203$) and stenting ($n = 88$), performed between 1 January 1991 and 31 December 1997, was analysed.

Results: Occlusive disease was significantly more likely than stenotic disease to be treated by primary stent deployment (19 of 88, 22 per cent) than PTA alone (11 of 203, 5 per cent) ($P < 0·01$, χ^2 test), as were lesions in the common iliac artery (common 69 of 214 (32 per cent) *versus* external 14 of 65 (22 per cent); $P < 0·05$, χ^2 test). Primary stent placement was associated with a significant increase in morbidity that delayed hospital stay (13 of 88 (15 per cent) *versus* seven of 203 (3 per cent); $P < 0·05$, χ^2 test). Emergency revascularization was required in four patients who underwent PTA (2 per cent) and two who had stenting (2 per cent) (P not significant).

Conclusion: Iliac stenting is associated with a significant increase in morbidity but with no improvement in symptomatic or haemodynamic outcome. These results do not justify the increased expense associated with the routine use of iliac stents.

Duplex surveillance does not enhance infrainguinal prosthetic bypass graft patency

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Background: All patients discharged from this unit with a patent infrainguinal polytetrafluoroethylene (PTFE) bypass are entered into a graft surveillance programme. Previous internal audit had suggested that duplex surveillance was not worthwhile in this patient group. The aim of this study was to compare the fate of infrainguinal PTFE grafts before and after stopping duplex surveillance.

Methods: Between January 1986 and December 1994, 220 grafts (141 above-knee popliteal, 69 below-knee popliteal, ten tibial) were entered into the duplex surveillance programme. Between January 1995 and June 1996, 56 further grafts (29 above-knee popliteal, 21 below-knee popliteal, six tibial) were followed prospectively without duplex scans.

Results: During the first study interval, an 'abnormal' scan was reported in 66 of 220 grafts. For clinical reasons (no further reconstruction feasible), no intervention was undertaken in 56 patients. Of these, 34 grafts occluded and 17 amputations were performed. An intervention to maintain patency was performed in ten patients. In 154 patients with 'normal' scans, 53 grafts occluded and 21 amputations were performed. During the second study interval, 20 grafts occluded and 12 amputations were performed. In six patients, an attempt was made to re-establish patency and this was successful in two. Kaplan–Meier 36-month primary and secondary patency rates were 48 and 51 per cent respectively for the group that underwent duplex surveillance, and 58 and 60 per cent for the group that was followed without duplex imaging.

Conclusion: Prospective duplex surveillance of infrainguinal PTFE bypass grafts does not enhance graft patency and cannot be justified.

Caval filters are an underexploited therapy for acute pulmonary embolism

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Background: Inferior vena caval filters are a recognized intervention for recurrent pulmonary embolism (PE). Filter utilization in the UK is considerably less than in Europe; this may partly be due to omission of referral of appropriate patients.

Methods: A cohort with the prospect of benefit from caval filter insertion was identified by retrospective study of inpatients who died within 30 days of a positive ventilation-perfusion (V/Q) scan over 2 years. The number of actively managed patients in this group who fulfilled the recognized criteria for caval filter insertion was determined.

Results: Fifty-two of 606 patients died within 30 days of scanning. Information was available on 38 (73 per cent) of 52 who had 39 scans (14 positive, 22 negative, three indeterminate). Six of 14 patients (two men and four women, aged 46–84 years) with a positive scan had strong indications for caval filter deployment including contraindication to anticoagulation (three), recurrent PE despite adequate anticoagulation (two) and complications arising from anticoagulation (one). All six died following continuing embolism or complications from anticoagulation.

Conclusion: Six of 14 patients who died following acute PE required caval filtration but were not offered this intervention. Failure to refer patients who would benefit from filtration may partially account for the disparity in utilization of caval filters between the UK and Europe. Furthermore, because of the choice of death as outcome marker, this study underestimated the value of caval filter utilization.

Duplex ultrasonography overestimates internal carotid artery stenosis in the presence of contralateral disease

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Background: Duplex ultrasonography is increasingly used as the only investigation before endarterectomy for internal carotid artery stenosis. Contralateral disease is present in approximately 20 per cent of these patients and may lead to overestimation of the carotid stenosis by duplex imaging before surgery. This problem was investigated in the present study.

Methods: Peak systolic and diastolic duplex velocities were compared with angiographic data before 126 consecutive carotid endarterectomies (106 symptomatic, eight asymptomatic, 12 precoronary revascularization). Some 3 months later velocities were repeated to assess whether endarterectomy of a diseased carotid artery affected contralateral velocity measurements.

Results: Significant contralateral carotid disease was present in 36 (29 per cent) of the 126 preoperative angiograms (14 occlusions, 22 stenoses greater than 60 per cent). Three months after operation 119 of the endarterectomy sites were widely patent. Duplex ultrasonography of the 105 non-operated patent contralateral arteries showed a decrease in mean(s.d.) peak systolic and diastolic velocities from 1·21(0·83) and 0·41(0·29) m s^{-1} before operation to 1·08(0·69) and 0·35(0·24) m s^{-1} respectively ($P < 0·01$, paired *t* test). Preoperative duplex velocities had indicated contralateral disease of greater than 50 per cent stenosis in 34 cases, but 14 of these were reclassified to less severe disease following surgery. Thirteen of these had been correctly classified by preoperative angiography while use of systolic and diastolic internal/common carotid artery velocity ratios reduced the overestimation of stenosis in eight of the 14 cases.

Conclusion: Bilateral carotid artery disease is common and may lead to overestimation of stenosis by duplex ultrasonography, which should therefore be supplemented with other modes of imaging.

Isolated femoral profundoplasty with endarterectomized superficial femoral artery for limb salvage in the elderly

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Background: This longitudinal observational study was designed to show that isolated profundoplasty to relieve a significant stenosis is a valid procedure for limb salvage in the elderly.

Methods: Twenty-seven patients with critical limb ischaemia underwent isolated profundoplasty using endarterectomized superficial femoral artery as an arterial patch. Nineteen patients were men The mean age was 72 (range 65–79) years. All patients had rest pain with or without an ischaemic foot ulcer or pedal gangrene.

Results: There was no operative death or immediate operative failure. All 27 limbs were improved, with relief of rest pain, healing of ulcers and healing after minor foot amputations. The 27 patients underwent a mean of 30 (range 12–45) months of periodic observation in an outpatient clinic, either to the present time or until death. Two patients required late amputations and one a femorodistal bypass.

Conclusion: Isolated profundoplasty has a place in leg revascularization in the high-risk elderly patient. Endarterectomized superficial femoral artery as a patch has the advantages of almost universal availability and anatomical convenience.

Limb salvage in the octogenarian

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Background: Critical limb ischaemia (CLI) presents a unique set of problems in the elderly patient. Foremost among these is the much greater likelihood of loss of independence and reduced quality of life if major amputation is required. For this reason it has been this unit's policy to attempt reconstructive vascular surgery in almost all cases of CLI. The outcome of this policy was examined.

Methods: All patients had surgery performed under one consultant and data were entered prospectively on to a database.

Results: Risk factors included diabetes (17 per cent), smoking (78 per cent) and ischaemic heart disease (31 per cent). Some 127 patients had either femoropopliteal (59), femorodistal (64) or popliteal–distal grafts (four) performed for limb-threatening ischaemia. Follow-up was performed at 3, 6 and 12 months and then at annual intervals until death. Seventeen of these patients required a subsequent major amputation, 12 at the below-knee and five at the above-knee level. Mean follow-up was 2 years. The perioperative mortality rate was 15 per cent, although eight of these patients were admitted with acute or chronic ischaemia. Cumulative graft secondary patency rate was 68 per cent at 4 years for vein grafts. Some 95 per cent of patients with patent grafts were independently mobile.

Conclusion: Excellent results can be achieved for limb salvage with a relatively low morbidity in this group. Elderly patients with CLI do not live long and avoidance of amputation is particularly desirable in order to maximize the quality of their remaining life.

Review of 94 tibial bypasses for intermittent claudication

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Background: The management of intermittent claudication is usually non-operative. Most surgeons accept, however, that intervention may be warranted for those with debilitating symptoms. Such interventions are limited to above-knee bypass or balloon angioplasty. However, the authors have performed almost 4500 bypasses for limb salvage, with careful audit of results, and suggest that, in very carefully selected cases, tibial bypass can also be performed for intermittent claudication. The present study aimed to review the results of infrainguinal bypass in this unit; to compare the results for above-knee, below-knee popliteal and tibial bypass in claudicants using either *in situ* or excised vein as the conduit; and to examine the indications and long-term follow-up for those undergoing tibial bypass for claudication.

Methods: A database has been maintained prospectively in this unit since 1986. Details of all patients undergoing infrainguinal bypass for claudication were retrieved. In-hospital charts were also reviewed and cross-referenced with the computer database. In addition to demographic details, data were extracted on operative indication and procedure, postoperative complications, return to desired level of activity and long-term graft patency.

Results: From 1987 to 1997, 409 infrainguinal reconstructions were performed for intermittent claudication (9 per cent of all infrainguinal reconstructions). Of these 73 per cent were in men and 27 per cent in women with a mean age of 64 (range 24–91) years. The operative procedures comprised 165 above-knee popliteal grafts, 150 bypasses to the below-knee popliteal artery and 94 to tibial arteries. There were no operative deaths. However, one of 165 patients who had an above-knee popliteal graft underwent an amputation. Primary and secondary patency rates at 4 years were 62 and 64 per cent for above-knee popliteal bypass, 77 and 81 per cent for below-knee popliteal bypass, and 86 and 90 per cent for tibial bypass. Cumulative survival was 93 per cent at 4 years.

Conclusion: Tibial bypass for severely disabling claudication can be performed with minimal morbidity and mortality rates, and is at least as durable as more commonly performed bypasses. These data indicate that concern over limb loss, death and limited life span may be exaggerated.

Two-year follow-up after acute thromboembolic lower limb ischaemia: the importance of continuing warfarin treatment

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of the Vascular Surgical Society

Background: The Vascular Surgical Society carried out an audit of follow-up after acute thromboembolic lower limb ischaemia.

Methods: The audit of acute lower limb ischaemia was done between 1 January and 31 March 1996 and included 474 patients. This report describes a 2-year follow-up of patients with a diagnosis of thrombosis or embolism who survived 30 days. Details were obtained for 214 (75 per cent) of 287 patients: half (107) were men, and the age range was 21–96 (mean 74) years.

Results: Amputation of the leg affected initially had been required (after 30 days) in 12 per cent. Further acute leg ischaemia had occurred in 11 per cent, and 9 per cent had undergone arterial reconstruction (11), angioplasty (seven) or thrombolysis (two). Major medical events were reported in 31 per cent and 35 per cent had died during the 2-year period. After the episode of acute ischaemia, warfarin was started in 57 per cent of patients, but was continued in only 43 per cent. Reasons for stopping were seldom known, nor was duration of treatment (range 1–22 (median 6) months in reported cases). Significantly more patients who were not on warfarin suffered recurrent acute limb ischaemia (19 *versus* 3 per cent; $P < 0{\cdot}01$). No significant association was found between recurrent acute ischaemia and initial diagnosis of embolism, thrombosis or atrial fibrillation (but numbers of recurrences in each group were small).

Conclusion: The incidence of recurrent acute thromboembolic limb ischaemia up to 2 years was significantly lower in patients treated with warfarin. Warfarin treatment is often stopped for no clear reason, especially in the elderly. Explicit advice about long-term warfarin therapy should be given when these patients are discharged from hospital.

Non-steroidal anti-inflammatory drugs to treat abdominal aortic aneurysm

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Background: Prostaglandin E_2 (PGE_2) and inflammatory cytokine levels are raised in the wall of abdominal aortic aneurysms (AAAs) and inflammatory processes appear to contribute to aneurysm expansion. The effect of PGE_2 on aortic smooth muscle cells (SMCs) and the influence of indomethacin on AAA growth and production of inflammatory mediators were investigated.

Methods: Proliferation and apoptosis of aortic SMCs cultured with PGE_2 were assessed by 5-bromo-2′-deoxyuridine uptake and oligonucleosome enzyme-linked immunosorbent assay. Full-thickness AAA explant cultures were used to measure the secretion of PGE_2, interleukin (IL) 1β and IL-6 in the presence and absence of indomethacin. In a case–control study, the effect of non-steroidal anti-inflammatory drugs (NSAIDs), including indomethacin, on AAA growth was examined.

Results: PGE_2 suppressed proliferation (IC_{50} 6 ng ml^{-1}) and increased apoptosis of aneurysm SMCs. Indomethacin diminished secretion of PGE_2, IL-1β and IL-6 by AAA explants (see Table below). The median AAA growth rate of 19 patients taking NSAIDs was 1·8 (range 0–11·2) mm per year compared with 3·2 (0·4–10·9) mm per year in 59 patients (matched for age, sex, smoking and initial AAA diameter) not taking these drugs ($P = 0{\cdot}004$).

	Control	Indomethacin (10 µmol l^{-1})	*P*
PGE_2 (ng ml^{-1}) ($n = 6$)	320 (63–576)	3 (2–6)	0·028
IL-1β (pg ml^{-1}) ($n = 5$)	190 (66–241)	8 (0–19)	0·04
IL-6 (ng ml^{-1}) ($n = 6$)	119 (33–267)	57 (22–144)	0·028

Values are median (range) levels in explant conditioned media at 96 h

Conclusion: PGE_2 is produced in the AAA wall in concentrations that are detrimental to SMCs. Indomethacin reduces PGE_2, IL-1β and IL-6 synthesis in aneurysm tissue and NSAIDs appear to reduce AAA growth. These drugs warrant further consideration for the treatment of AAA.

Angiogenesis and the atherosclerotic carotid plaque: association between symptomatology and plaque morphology

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Background: Symptomatic carotid disease due to thromboembolism has been associated with acute plaque instability and intraplaque haemorrhage. These features may be influenced by the fragility and position of plaque neovessels. The purpose of this study was, therefore, to determine whether any association existed between neovessel density, position, morphology and thromboembolic sequelae.

Methods: Carotid endarterectomy (CEA) samples were collected from 15 asymptomatic patients with greater than 80 per cent stenosis and from 13 patients with greater than 80 per cent stenosis and symptoms within 30 days of CEA. Groups were matched for sex, age, risk factors and plaque size. Samples were stained with haematoxylin and eosin, and Van Gieson stains. An endothelial-specific antibody to CD31 was used for immunohistochemistry. Plaques were assessed for histological characteristics while neovessels were counted and characterized by size, site and shape.

Results: There were more neovessels in plaques ($P < 0{\cdot}00001$) and fibrous caps ($P < 0{\cdot}0001$) from symptomatic than asymptomatic patients. Symptomatic plaque neovessels were larger in size ($P < 0{\cdot}004$) and more irregular in shape. There was a significant increase in plaque necrosis and rupture in symptomatic plaques. Plaque haemorrhage and rupture were associated with more neovessels within the plaque ($P < 0{\cdot}02$, $P < 0{\cdot}001$) and fibrous cap ($P < 0{\cdot}05$, $P < 0{\cdot}004$). Patients with preoperative or intraoperative embolization had more plaque and fibrous cap neovessels ($P < 0{\cdot}03$, $P < 0{\cdot}001$).

Conclusion: Symptomatic carotid disease is associated with increased neovascularization within the atherosclerotic plaque and fibrous cap; these vessels appear larger in size, more irregular in shape and may contribute to plaque instability and onset of thromboembolic events.

Patients with a failed infrainguinal bypass graft have abnormal lipid metabolism

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Background: Dyslipidaemias adversely affect vascular tone, endothelial function and platelet activation. Abnormal lipid metabolism has not been established as a risk factor for infrainguinal bypass graft failure. Lipid metabolism was evaluated prospectively in patients with patent and occluded grafts.

Methods: Twenty-eight patients with failed infrainguinal grafts (group 1) were identified from a prospective computerized database. Twenty matched controls with functioning grafts (group 2) were recruited from a graft surveillance programme. Fasting blood samples were analysed for triglyceride (TG), high-density lipoprotein (HDL) and cholesterol. A newly devised rapid TG tolerance test was conducted with analysis of TG at 1, 2 and 2·5 h. Endothelial lipoprotein lipase (LPL) was measured 30 min after intravenous administration of heparin 50 units kg^{-1}.

Results: The cholesterol : HDL ratio was significantly higher in group 1 than group 2 (median 6·0 (range 3·1–10·0) *versus* 4·7 (2·3–9·4); $P = 0{\cdot}0008$, Mann–Whitney test) as was fasting TG (2·6 (1·0–6·3) *versus* 1·7 (0·6–4·7) mmol l^{-1}; $P = 0{\cdot}03$). The area under the curve of the TG tolerance test was not significantly different ($P = 0{\cdot}08$); however, the 2·5-h levels of TG were significantly different between the groups (group 1, 2·0 (0·5–6·6) mmol l^{-1}; group 2, 1·2 (0·3–6·8) mmol l^{-1}; $P = 0{\cdot}01$). LPL was significantly lower in group 1 (52·4 (2·2–235·9) *versus* 86·8 (28·6–281·5) mmol/l; $P = 0{\cdot}04$).

Conclusion: These data suggest that abnormal lipid metabolism is a significant risk factor for infrainguinal graft occlusion. This study provides a rationale for randomized trials of lipid-modifying therapies in patients undergoing arterial reconstruction for peripheral vascular disease.

Uptake of tetracycline in aortic aneurysms: influence on inflammation and proteolysis

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Background: Derivatives of tetracycline (TC), through their inhibition of matrix metalloproteinases (MMPs), have been suggested as potential medical therapy to limit growth of abdominal aortic aneurysms (AAAs), but penetration of the aortic wall *in vivo* has not been demonstrated. The uptake and concentration of TC in aneurysm wall, and its effect on MMP and cytokine production, were investigated.

Methods: Patients undergoing elective AAA repair ($n = 5$) were given a single bolus of intravenous TC 500 mg on induction of anaesthesia. The TC concentrations achieved in serum, aneurysm wall and mural thrombus were determined using a microbiological assay In separate patients, not given TC, AAA biopsy explants were established and the effect of TC (0, 10 and 100 µg ml^{-1}) on hydroxyproline, MMP-9 and cytokine (MCP-1 and interleukin (IL) 6) secretion were investigated using colorimetric assays and immunoassays.

Results: At the time of aortic cross-clamping median TC concentration was 9 (range 5–12) µg ml^{-1} in serum, 2·7 (1·3–9·6) µg g^{-1} in AAA wall and nil in mural thrombus (see *Table*).

	TC (µg ml^{-1})		
	0	10	100
Hydroxyproline (µg ml^{-1}) ($n = 6$)	31·2 (21·7–41·3)	34·2 (13·0–40·1)	30·7 (23·3–33·4)
MMP-9 (ng ml^{-1}) ($n = 6$)	20·9 (4·8–38·5)	10·1 (2·1–26·1)	2·8 (0–12·8)*
MCP-1 (ng ml^{-1}) ($n = 7$)	49 (11–96)	58 (46–97)	6 (2–25)†
IL-6 (ng ml^{-1}) ($n = 7$)	132 (109–192)	104 (50–218)	119 (45–277)

Values are median (range) secretion by AAA explants. *$P = 0{\cdot}043$, †*$P = 0{\cdot}018$ (Wilcoxon signed rank test)

Conclusion: TC rapidly penetrates AAA wall *in vivo* and inhibits MMP-9 and MCP-1 release by AAA explants. This suggests that TCs have the potential to limit aneurysm growth.

Platelet function during carotid endarterectomy and the antiplatelet effect of dextran 40

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Background: Dextran 40 has been shown to reduce cerebral embolization following carotid endarterectomy (CEA). This study aimed to determine changes in platelet function during CEA and the antiplatelet effect of dextran 40.

Methods: Platelet function was measured by whole-blood flow cytometry in the peripheral arterial blood of patients during CEA and 24 h later. The binding index of P-selectin and PAC-1 expression were measured as markers of activation and aggregation. Patients were kept on aspirin 75–150 mg until the day of surgery and received an intravenous bolus of 5000 units unfractionated heparin before carotid artery clamping. High-intensity transient signals (HITS) in the ipsilateral middle cerebral artery were measured with transcranial Doppler (TCD) ultrasonography before, during and after operation. Results are presented as median (interquartile range) and statistical significance was determined using the Mann–Whitney *U* test.

Results: Thirty-eight patients undergoing CEA were studied. The P-selectin binding index rose significantly from incision (0·9 (0·2–2·7)) after carotid clamping (1·5 (0·6–3·6); $P < 0{\cdot}01$), clamp release (1·7 (0·3–3·0); $P < 0{\cdot}01$), 1 h after operation (1·5 (0·3–2·6); $P < 0{\cdot}05$) and 24 h after operation (1·3 (0·6–2·5); $P < 0{\cdot}05$). PAC-1 binding index increased from incision (0·4 (0·1–0·8)) after carotid clamping (2·0 (0·4–4·2); $P < 0{\cdot}01$) and clamp release (1·8 (0·3–2·9); $P < 0{\cdot}05$). TCD monitoring showed an increase in preoperative HITS per 30 min (2 (0–3)) during dissection (8 (1–15), $P < 0{\cdot}05$), after clamp release (16 (2–27); $P < 0{\cdot}01$) and during recovery (10 (2–29), $P < 0{\cdot}01$). After operation, patients with more than 50 HITS per 30 min were started on an infusion of dextran 40. Six patients had a dextran 40 infusion. The P-selectin binding index decreased from 1·6 (0·7–1·9) to 0·6 (0·3–1·5) 1 h after dextran ($P < 0{\cdot}05$) and 0·1 (0·1–0·2) 24 h after dextran ($P < 0{\cdot}05$). PAC-1 expression decreased from 0·4 (0·3–0·5) to 0·1 (0·1–0·1) 24 h after dextran ($P < 0{\cdot}05$).

Conclusion: Significant platelet activation and aggregation occurs during CEA despite the use of antiplatelet treatment. A simultaneous increase in HITS was demonstrated with TCD. Dextran 40 was shown to have an antiplatelet effect after CEA; this is further evidence that it may have a role in reducing thromboembolic complications.

Angioplasty reverses the systemic effects of exercise in intermittent claudication

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Background: The choice between exercise training and percutaneous transluminal angioplasty (PTA) in the treatment of intermittent claudication (IC) remains controversial. Exercise is known to induce systemic effects in claudicants. This study aimed to determine whether such systemic effects are reversed by PTA.

Methods: Ten patients with IC were recruited before PTA. Having emptied the bladder and rested for 1 h, pre-exercise blood and urine samples were collected. Patients underwent treadmill exercise to their maximum walking time and further blood samples were collected at 10, 20 and 30 min. A second urine sample was collected at 60 min. Total antioxidant capacity (TAC) and von Willebrand factor (vWF) were measured in blood, and albumin : creatinine ratio (ACR) and retinol binding protein : creatinine ratio (RBP : Cr) in urine. Patients were recalled 2 weeks after successful angioplasty and the protocol was repeated. Statistical analysis was by Wilcoxon signed rank test.

Results: Following PTA, all patients walked for 5 min on the treadmill. All patients had a significant exercise-induced fall in ankle pressure that was reversed by PTA Changes in TAC are shown in the *Table*. There was no significant change in vWF. Exercise in claudicants induced a significant increase in median ACR (pre/post exercise (pre-exercise value divided by post-exercise value) 0·8; $P = 0{\cdot}03$) and in median RBP . Cr (pre/post exercise 1·8; $P = 0{\cdot}04$). These changes were no longer evident after successful PTA.

	Before exercise	Time after exercise (min)		
		10	20	30
Before PTA	1·30(0·17)	1·41(0·14)	1·35(0·27)	1·34(0·18)
After PTA	1·27(0·10)	1·27(0·10)	1·26(0·08)	1·27(0·11)

Values are mean(s.d.) total antioxidant capacity. $P \leq 0{\cdot}05$, before *versus* after PTA at all time intervals

Conclusion: Exercise-induced changes in renal glomerular (ACR) and tubular function (RBP : Cr) in claudicants were reversed by successful angioplasty. PTA reduced the systemic TAC before and after exercise suggesting a reduced free radical challenge.

Fifteen years of experience using 6 cm as a criterion for abdominal aortic aneurysm surgery

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Background: One criterion for abdominal aortic aneurysm (AAA) surgery in the authors' unit is aneurysm diameter of 6 cm. The impact of applying this criterion on surgical workload and rupture rate was analysed.

Methods: Some 584 consecutive patients with an AAA of 3 cm or greater presenting to this unit since 1984 have had the following criteria for considering surgery applied prospectively: a diameter of 6 cm, an expansion rate of more than 1 cm per year, or symptoms.

Results: Forty-three patients had an AAA of 6 cm or greater on initial presentation and would have been treated in the same way, if a smaller diameter was used. Sixty-eight patients had an AAA that expanded to 6 cm on observation with ultrasonography over the period of up to 15 years. The total number of patients with a 6-cm AAA was therefore 111. Of the 541 aneurysms that were under 6 cm at the initial scan, 454 were followed with ultrasonography. Some 343 reached 4 cm and 204 reached 5 cm. Operating at 5 cm therefore would have doubled the potential workload, and 4 cm would have tripled it. During the 15 years, 24 (4 per cent) of the 584 AAAs ruptured. Of these 24 patients, 12 were unfit for surgery, five declined operation or follow-up, the aneurysm ruptured beforehand in three who were booked for an operation or outpatient visit, and four failed to reach the operative criteria before rupture occurred. Rupture could therefore possibly have been prevented in seven (1 per cent) of the 584 by operating at a smaller diameter. The reported mortality rate for planned surgery is 2–8 per cent.

Conclusion: By using these criteria for surgery, the workload is cut by half or more and the consequent risk of rupture is lower than the mortality rate associated with planned surgery.

Scottish Audit of Surgical Mortality, 1997

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Background: A national audit of surgical deaths can be seen as the final step in what has been termed the 'journey of care' for both the individual patient and for the population as a whole.

Methods: The Scottish Audit of Surgical Mortality (SASM) examines all hospital deaths in Scotland occurring while under the care of a surgical specialist and all deaths within 30 days of an operation.

Results: Compliance for the completion of forms relating to vascular deaths during the first 4 years of the SASM (1994–1997) has remained over 92 per cent. In 1997 the compliance was 97 per cent. These figures compare favourably with the other surgical specialties where the overall compliance for 1997 was 92 per cent. Some 14 per cent of the 4408 deaths reported in 1997 occurred in patients admitted with vascular disease, the majority (83 per cent) being emergency admissions. Of these 507 vascular deaths, 293 were postoperative; the remaining 214 patients did not undergo operation. This represents an improvement over the years 1994–1996 when vascular deaths numbered 554, 573 and 524 respectively. The mean age of the patients who died from vascular disease in 1997 was 73 (range 19–92) years. A consultant surgeon made the decision to operate in 98 per cent of the patients with vascular disease who died at operation and was the principal surgeon in 70 per cent of cases. Vascular consultants carried out a higher percentage of operations than their counterparts in other surgical specialties (general surgery, 63 per cent; mean for other subspecialties, 60 per cent). In the non-operative group of vascular deaths in 1997, a vascular consultant was in charge in 66 per cent of cases; the figure for operated cases was 87 per cent. Adverse factors were believed to contribute to death in 10 per cent of cases, but were considered a direct cause of death in fewer than 1 per cent.

Conclusion: These figures reflect the high quality of vascular services in Scotland, where there is a considerable consultant presence in the management of high-risk patients. This consultant involvement is higher than in other subspecialties and, bearing in mind the high percentage of emergencies, has significant resource implications for the delivery of vascular services.

Avoiding the complications of thrombolysis

S. M. Thomas and P. A. Gaines on behalf of the Thrombolysis Study Group

Background: NATALI is a voluntary database of patients undergoing peripheral vascular thrombolysis run on behalf of the Thrombolysis Study Group. The size of the data set allows analysis to identify predictors of outcome and complications. These may be patient factors or variables related to the technique used.

Methods: Since its inception on 1 January 1990, 798 thrombolytic events have been recorded. Details are collected on a wide range of factors: perceived risk factors; details of thrombolysis technique; complications; outcome; and adjunctive procedures. Using univariate and multivariate analysis, factors associated with an increased risk of complications were investigated.

Results: Death and complications (perilysis) occurred in 25 9 per cent of episodes ($n = 207$). Patient factors were the main influence on the risk of complications. Increasing age, use of aspirin and thrombolysis of grafts were significantly associated with an increased risk of complications after adjustment for confounders ($P < 0\ 05$). Female sex, the presence of peripheral vascular disease and Fontaine class were of borderline significance. Other patient factors were not associated with an increased risk of complication. Aspects of radiological technique, such as agent used, sheath size, length of lysis, dose of lysis, use of heparin or adjunctive procedures, had no relationship to the rate of complications.

Conclusion: Case selection is the most important factor influencing the occurrence of complications. Radiological technique does not seem to influence the occurrence of complications.

Results of the Carotid And Vertebral Artery Transluminal Angioplasty Study

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Background: Trials have demonstrated the benefit of surgery for severe carotid stenosis, but there is still significant morbidity from the operation. Percutaneous transluminal angioplasty (PTA) avoids general anaesthesia and trauma from a neck incision, but has not yet gained acceptance for carotid stenosis because of concern about the risks. The Carotid And Vertebral Artery Transluminal Angioplasty Study was established to investigate the risks and benefits of cerebrovascular PTA.

Methods: Twenty-four centres in Europe, Australia, Canada and the USA collaborated to randomize 504 patients (mean age 67 years; 69 per cent men) with carotid stenosis to surgery ($n = 253$) or angioplasty ($n = 251$) between 1992 and 1997.

Results: Some 90 per cent of the patients were recently symptomatic. PTA was carried out using balloon catheters with the adjunctive use of stents in 26 per cent. Mean carotid stenosis by the common carotid method was 87 per cent. Safety analysis by intention to treat showed no difference in the primary outcome measure of disabling stroke or death within 30 days of treatment (surgery, 6 per cent; PTA, 6 per cent). Cranial nerve injury and myocardial ischaemia were only reported at the time of treatment in the surgical group. Long-term survival curves showed no difference in ipsilateral stroke during follow-up.
Conclusion: Carotid surgery and angioplasty are equivalent in safety and efficacy, but angioplasty has advantages with respect to nerve injury and cardiac complications.

RETA: the registry of endovascular treatment of abdominal aortic aneurysms

S. M. Thomas, P. A. Gaines and J. D. Beard on behalf of the joint working party of the Vascular Surgical Society and British Society of Interventional Radiologists

Background: RETA is a voluntary registry within the UK established as a joint venture between radiologists and surgeons. The aim is to evaluate carefully the endovascular treatment of abdominal aortic aneurysms during introduction into clinical practice.
Methods: Some 367 patients have been included in the registry from 23 centres since its inception on 1 January 1996. In the majority (82 per cent) an elective repair was performed for an asymptomatic aneurysm. The mean age of the patients was 71·9 years and 28 per cent were deemed unsuitable for conventional repair. One hundred and ninety-nine bifurcated (54 per cent), 18 tube (5 per cent) and 148 aortouni-iliac with crossover (40 per cent) stent graft types were placed.
Results: At the end of the procedure 77 per cent of aneurysms were excluded with no complications. Twenty-one patients (6 per cent) required conversion to open repair. Forty-four (12 per cent) required additional endovascular procedures. At 30 days 87 per cent of the aneurysms were excluded or repaired. The 30-day mortality rate was 7 per cent ($n \doteq 24$) with a significant improvement between 1996 and 1997, from 11 to 4 per cent. There were 25 persistent leaks (7 per cent). The death rate was related to the fitness of patient, device used and requirement for conversion. One-year follow-up data are available for 140 patients. There have been 13 deaths (9 per cent), three ruptures (2 per cent) and some form of complication in 20 per cent of cases overall.
Conclusion: Improving results have been demonstrated for the primary procedure. At present there is a relatively high complication rate and ruptures have occurred. Rigorous continued follow-up is required.

Endovascular aneurysm repair: the need for randomized controlled trials

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Background: An audit of endovascular aneurysm repair (EVAR) was undertaken in order to assess the efficacy of this new approach in the treatment of abdominal aortic aneurysm.
Methods: An international register of EVAR was started in 1996, with emphasis on close follow-up.
Results: Data have now been accumulated for 895 cases. The 30-day mortality rate is low at 3 per cent; patients who died generally had major co-morbidity. At discharge 14 per cent were identified as having an endoleak (persistent blood flow outside the lumen of the endoluminal graft but within the aneurysm sac) and another 18 per cent developed new endoleaks during the first year of follow-up. Continued expansion of the aneurysm was observed in 22 per cent. This occurred in 53 per cent of patients with an identified endoleak compared with 11 per cent of those in whom no endoleak was demonstrated ($P < 0.01$). Aneurysm rupture after EVAR occurred in six patients, three of whom died.
Conclusion: That EVAR is technically feasible is beyond doubt. Close follow-up has identified problems specific to the minimally invasive approach. The significance of endoleaks in particular remains unclear, but the strong association with continued aneurysm expansion is of concern. The primary purpose of EVAR, however, is to prolong life and in this study the cumulative 2-year survival rate (including operative deaths) was 85 per cent. In patients without any complications the benefits of the minimally invasive approach are readily apparent. Thus, while there is no place for unrealistic optimism, there certainly appears to be a role for EVAR. To prevent inappropriate widespread application of this new approach, or indeed unwarranted condemnation, randomized controlled trials comparing EVAR with conventional management are essential.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

D-lactate as an early marker of intestinal ischaemia after ruptured abdominal aortic aneurysm repair

Sir

I read with interest the paper suggesting that D-lactate may be an early marker of intestinal ischaemia following repair of ruptured aneurysm. It is not clear from the methods whether the patients undergoing colonoscopy also had biopsy with histological assessment. If only visual assessment was made, this may not be accurate[1]. Second, I disagree with the suggestion that measurement of gut intramucosal pH is expensive. Sigmoid tonometry is in fact a very simple and inexpensive system of monitoring and is more likely to pick up even minor degrees of ischaemia.

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1 Welch M, Baguneid MS, McMahon RF, Dodd PD, Fulford PE, Griffiths GD *et al.* Histological study of colonic ischaemia after aortic surgery *Br J Surg* 1998; **85:** 1095–8.

Author's reply

Sir

We appreciate the interest expressed in our article by Mr Welch. The use of biospy was not explicitly noted, but all abnormalities on colonoscopy were biopsy proven and histologically evaluated. We disagree with the comment that the measurement of gut intramucosal pH is not expensive, especially when related to the measurement of a serum marker. The use of tonometry is a valuable and promising tool in the determination of bowel ischaemia but the costs are at present considerable. The costs for the tonometer catheter were originally £75 per catheter when the saline method was used. Nowadays, the catheters cost around £50 per catheter. The new Tonocap (Datex-Ohmeda, Helsinki, Finland) system costs around £5000. In comparison one measurement of D-lactate costs £5. Although the number of studies validating the old method for measuring intramucosal pH are considerable, the use of the Tonocap system has been less extensively validated. Although the measurement of intramucosal pH has potential as a good diagnostic tool, a critical appraisal is required.

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Repair of ventral hernias with expanded polytetrafluoroethylene patch

Sir

We congratulate Balén *et al.* (*Br J Surg* 1998; **85:** 1415–18) for confirming that excellent results can be achieved using expanded polytetrafluoroethylene (ePTFE) in ventral hernia repair. Some concerns have been expressed about this prosthesis which has a different structure from that of a mesh. This may be an advantage, particularly when a prosthesis has to be used in direct contact with the bowel or other viscera. We recently reviewed our experience[1] of 158 incisional hernia repairs using ePTFE patches implanted either in a retromuscular extraperitoneal site or intraperitoneally. In the extraperitoneal position efficacy was comparable to that of a mesh. In the intraperitoneal site tolerance was excellent and similar to the results of Balén *et al.* with no late obstructions, fistulas, or patch migrations in a mean follow-up of 37 (range 12–90) months. The drawback of ePTFE is the associated poor tissue ingrowth especially when the prosthesis is required to bridge a large defect. Techniques involving side-to-side suturing of an ePTFE patch have been used but are associated with a high rate of recurrent hernia attributed to weak attachment of the patch to the edges of the defect[2]. Balén *et al.* attribute their low recurrence rate to the technique of anchoring the prosthesis to the anterior aponeurosis using a running Gore-Tex CV3 (W. L. Gore, Arizona, USA) suture. Interrupted sutures might provide 'button-hole' recurrences as the first step of larger recurrences. We prefer to overlap the dorsal aspect of the edges of the defect with at least 5 cm of patch, secured in place by sutures. Refinements will probably come from composite meshes with a layer of submicronic pore size ePTFE on the visceral side providing good tissue ingrowth as well as reduced adhesion. The first clinical series of 30 patients using a composite mesh (polypropylene-ePTFE) has been published[3]. The recurrence rate in this series is comparable to that of Balén *et al.* and ourselves. Surgeons are impatient to test a composite mesh as soon as it becomes available in Europe.

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1 Gillion JF, Bégin GF, Marecos C, Fourtanier G. Expanded polytetrafluoroethylene patches used in the intraperitoneal or extraperitoneal position for repair of incisional hernia of the anterolateral abdominal wall. *Am J Surg* 1997; **174:** 16–19
2 Ambrosiani N, Harb J, Gavelli A, Huguet C. Echec de la cure des éventrations et des hernies par plaque de ePTFE (111 cas). *Ann Chir* 1994, **48:** 917–20.
3 Bendavid R. Composite mesh (polypropylene-ePTFE) in the intraperitoneal position. A report of 30 cases *Hernia* 1997; **1:** 5–8.

Author's reply

Sir

I thank Dr Gillion for his comments and mainly agree with his observations on the good results that can be obtained with ePTFE used to repair incisional hernias, especially if there is to be contact with the bowel. In another institution I used the same technique with polypropylene mesh and running sutures (because of the cost of ePTFE) and results were excellent. There was no recurrence in over 40 patients in whom the bowel was protected from the mesh by the peritoneum. I believe that not only ePTFE but the surgical technique employed play a part. I agree that the mesh or patch should be overlapped more than 3 or 4 cm with healthy abdominal wall, either underneath or over the musculoaponeurotic layer. I think it is easier and quicker to do it over the fascia. If absorbable material is used to suture non-absorbable mesh there is a high risk of misplacement of the mesh and hernia recurrence, and polypropylene mesh left in contact with the bowel sometimes produces intestinal perforation, especially when it is used under septic conditions in the lower abdomen.

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Bilirubin and peripheral vascular disease

Sir

We read with interest the report by Nicholl *et al* (*Br J Surg* 1995; **82**: 1561–2, abstract) concerning the association between low serum bilirubin and peripheral vascular disease which has been explained by the perception that bilirubin is a naturally occurring antioxidant[1,2]. A low bilirubin concentration is thought to prevent solubilization of cholesterol through the bile and increase serum cholesterol concentrations. There was, however, no accurate control group in the study by Nicholl *et al.* We compared prospectively serum bilirubin and cholesterol values between 30 patients with peripheral vascular disease (11 women, 19 men; median age 75 (range 56-88) years) and 30 age- and sex-matched control patients. The ankle : brachial index was tested in patients (mean index value 0·52) and controls (mean index value 1·14), excluding possible latent vascular disease. Patients with gallstones or liver disease and malignancy were excluded from both groups.

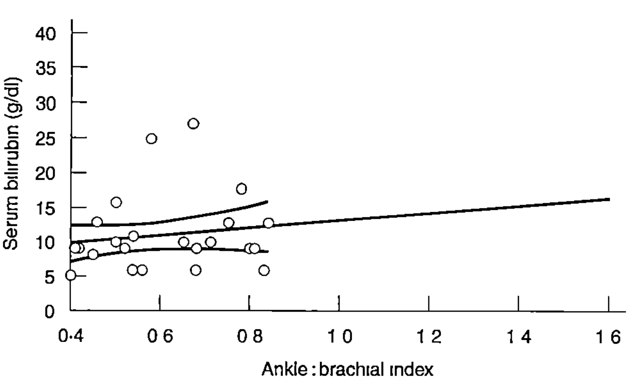

Fig. 1 Relationship between serum bilirubin and ankle : brachial index in 30 patients with peripheral vascular disease

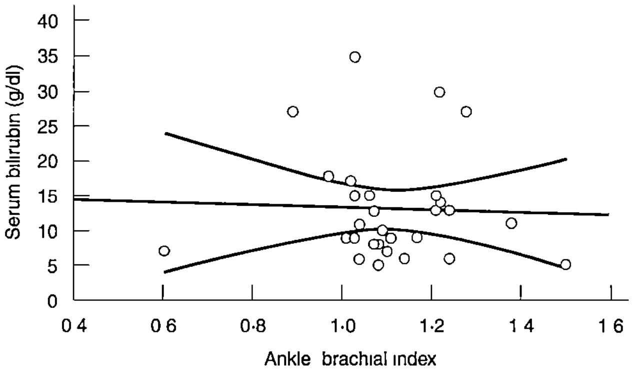

Fig. 2 Relationship between serum bilirubin and ankle : brachial index in 30 control patients

The median concentration of serum bilirubin in patients with vascular disease was 10 g/dl compared with 13 g/dl in the control group (*P* not significant) (linear regression analysis did not show a correlation between low serum bilirubin and the ankle : brachial index). Median concentration of cholesterol in patients with vascular disease was 5 7 mmol/l compared with 5·0 mmol/l in controls (*P* not significant). We concluded that serum bilirubin has no value as a marker of the severity of peripheral vascular disease.

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1 Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. Bilirubin is an antioxidant of possible physiological importance *Science* 1987; **235**: 1043–6.
2 Stocker R, Glazer AN, Ames BN. Antioxidant activity of albumin-bound bilirubin *Proc Natl Acad Sci U S A* 1987; **84**: 5918–22.

Comparison of POSSUM and the Portsmouth predictor equation for predicting death following vascular surgery

Sir

We read with interest the paper by Wijesinghe *et al.* (*Br J Surg* 1998; **85**: 209–12) which compared predicted death using the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) and the Portsmouth predictor equation for mortality (P-POSSUM). It is evident from this article that the application of the linear and exponential methods to the above equations produce different predicted results for the same group of patients.

In the linear method of analysis the risk for each mortality group is artificially taken to be the median in that group. Although this applies well to high-risk patients, it overpredicts death in the low-risk population, as illustrated in the below 10 per cent mortality group where predicted mortality is taken to be 5 per cent. In the linear method used by Whiteley *et al.*[1], employing the POSSUM equation, different mortality bands were used and the risk of each band was calculated as the mean of the predicted mortality for each patient in that group.

The exponential method of analysis used by Copeland *et al.*[2] was not described in the original POSSUM article and was therefore not open to critical review. Wijesinghe *et al.* currently highlight the drawbacks of this method. Whereas this method yields reasonable results using the POSSUM equation it produces spurious results when using the P-POSSUM. It would be useful to know whether these differences are statistically significant.

Both methods have limitations and cannot be safely relied on unless a standard methodology is devised that can be applied to both POSSUM and P-POSSUM equations.

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1 Whiteley MS, Prytherch DR, Higgins B, Weaver PC, Prout WG. An evaluation of the POSSUM surgical scoring system. *Br J Surg* 1996; **83**: 812–15.
2 Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *Br J Surg* 1991; **78**: 356–60.

Water-soluble contrast study predicts the need for early surgery in adhesive small bowel obstruction

Letter 1

Sir

The paper by Chen *et al.* (*Br J Surg* 1998; **85**: 1692–4) may be somewhat misleading in that they designed and recruited for a randomized controlled trial of the diagnostic and therapeutic role of Gastrografin (Schering, Berlin, Germany) in adhesive small bowel obstruction (ASBO). Diagnosis was not always straightforward. The authors described criteria for diagnosis but the qualification of complete and incomplete (or early complete) ASBO was not attempted. They did not differentiate patients who had undergone a previous lower abdominal laparotomy despite evidence suggesting that this predisposes to failure of resolution and that it can be dangerous to delay surgery[1]. The patients were subjected to up to five radiographs in the first 24 h. Busy public hospitals often have inevitable delays in radiology departments and clinical review. This may explain the high rate of bowel resection in this study (six of 47) despite the high overall rate of operation (29 per cent) when others have shown that nearly 90 per cent of ASBOs resolve spontaneously[2].

Gastrografin stimulates the gut at both ends and the possible mechanisms of its action in ASBO are reiterated by Chen *et al.* Gastrografin has been extensively utilized in diagnostic radiology with an excellent safety record for many years and no safety problems have been described on Gastrografin's role in ASBO in the present study and in others[3,4].

An obvious synthesis of this information is as follows. (1) Previous single lower abdominal incisions in a patient with clinical and radiographic evidence of ASBO should lower the threshold for early operation. (2) Those who have had multiple laparotomies or have diagnostic confusion may benefit from the diagnostic and possible therapeutic properties of Gastrografin. (3) This group of patients require regular clinical review, not frequent trips to the radiology department.

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1 Meagher AP, Moller C, Hoffinan DC. Non-operative treatment of small bowel obstruction following appendicectomy or operation on the ovary or tube. *Br J Surg* 1993; **80**: 1310–11.
2 Brolin RE. Partial small bowel obstruction. *Surgery* 1984; **95**: 145–9
3 Assalia A, Schein M, Kopelman D, Hirshberg A, Hasmonai M Therapeutic effect of oral Gastrografin in adhesive, partial small-bowel obstruction: a prospective randomized trial. *Surgery* 1994; **115**: 433–7.
4 Feigin E, Seror D, Szold A, Carmon M, Allweis TM, Nissan A *et al.* Water-soluble contrast material has no therapeutic effect on postoperative small-bowel obstruction: results of a prospective, randomized clinical trial *Am J Surg* 1996; **171**: 227–9.

Letter 2

Sir

We read with interest the article by Chen *et al.* We suggest, however, that carrying out serial plain films after the initial administration of contrast over the next 24 h is excessive and unnecessary in the majority of patients.

Recent data from our own unit that prospectively compared water-soluble contrast radiology with plain radiology in 62 patients with suspected small bowel obstruction, was based on delayed films at 90 min and 4 h after ingestion. Failure of contrast to reach the colon was demonstrated in eight of 24 patients receiving contrast, all of whom went to surgery and all had proven small bowel obstruction.

We would therefore entirely agree with Chen *et al.* that a water-soluble contrast study is helpful in predicting the need for surgery in small bowel obstruction, but suggest that the decision can be made after the 4-h radiograph and that repeated films thereafter are probably unnecessary.

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Authors' reply

Sir

We thank Spillane and Paterson-Brown *et al.* for their interest in our study. Patients whose contrast medium reached the ascending colon within the first 24 h were considered as having incomplete ASBO. Our results showed that patients with ASBO who had undergone previous upper or lower abdominal surgery had the same resolution rate. Patients with previous lower abdominal surgery had a longer time interval to develop ASBO.

Early appropriate treatment of ASBO by conservative means or surgical intervention may prevent prolonged hospitalization or complications of delayed surgery[1–3]. Water-soluble contrast study is an easy, effective and simple method to determine the need for surgery in patients with ASBO as shown in this study as well as another[4]. Another cost-effectiveness study to compare the results of water-soluble contrast examination with regular clinical review is needed.

The data from Paterson-Brown *et al.* is similar to a recent report[4] showing that surgical intervention should be performed if the contrast medium fails to reach the colon within 4 h of ingestion. However, another study showed that eight of 42 patients in whom the contrast medium failed to empty into the colon within 8 h were successfully treated with non-operative methods[5]. Our concern is that if patients can benefit from non-operative treatment, surgical intervention is unnecessary. It has been reported that patients with ASBO may be treated non-operatively for 12–48 h if there are no signs of strangulation[6–8]. Our study suggests that patients with ASBO in whom contrast medium failed to reach the colon within 24 h should receive surgical intervention.

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1 Sarr MG, Bulkley GB, Zuidema GD. Preoperative recognition of intestinal strangulation obstruction. Prospective evaluation of diagnostic capability. *Am J Surg* 1983; **145:** 76–82.
2 Deutsch AA, Eviatar E, Gutman H, Reiss R Small bowel obstruction: a review of 264 cases and suggestions for management. *Postgrad Med J* 1989; **65:** 463–7
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4 Chung CC, Meng WCS, Yu SCH, Leung KL, Lau WY, Li AKC. A prospective study on the use of water-soluble contrast follow-through radiology in the management of small bowel obstruction. *Aust N Z J Surg* 1996; **66:** 598–601.
5 Chen SC, Chang KJ, Lee PH, Wang SM, Chen KM, Lin FY. Oral Urografin in postoperative small bowel obstruction *World J Surg* (in press).
6 Brolin RE, Krasna MJ, Mast BA. Use of tubes and radiographs in the management of small bowel obstruction *Ann Surg* 1987; **206:** 126–33
7 Hofstetter SR Acute adhesive obstruction of the small intestine. *Surg Gynecol Obstet* 1981; **152:** 141–4.
8 Assalia A, Schein M, Kopelman D, Hirshberg A, Hasmonai M Therapeutic effect of oral Gastrografin in adhesive, partial small bowel obstruction: a prospective randomized trial. *Surgery* 1994; **115:** 433–7.

Sodium fusidate and the cytokine response in an experimental model of acute pancreatitis

Sir

I am concerned that there may be serious flaws in the work of Osman *et al.* (*Br J Surg* 1998; **85:** 1487–92). Sodium fusidate is an antibiotic and therefore there should have been a third 'control' group which included an antibiotic with a similar spectrum of activity but without the immunomodulatory effect. Treatment was given before induction of acute pancreatitis and not after, which is more relevant clinically. There is no difference in mortality: six of ten is not significantly different from three of 10 (Fisher's exact test, $P = 0.18$ (one-tailed), $P = 0.37$ (two-tailed)). The conclusion cannot be justified by the results.

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Laparoscopic subtotal cholecystectomy in patients with complicated acute cholecystitis or fibrosis

Sir

We welcome the paper by Michalowski *et al.* (*Br J Surg* 1998; **85:** 904–6) advocating laparoscopic subtotal cholecystectomy (LSC) as an alternative procedure to prevent ductal injury when laparoscopic total cholecystectomy may be unsafe. We are concerned, however, that the paper encourages unwise perseverance in difficult circumstances, contrary to the common practice of converting to open surgery to minimize operative complications[1]. Furthermore, the authors failed to highlight some of the inherent problems of LSC. In our experience, residual or new stone or sludge formation and external biliary fistula have complicated these partial resections, particularly where a residual Hartmann's pouch is resutured. These patients then need an open exploration, which with hindsight could have been saved by conversion. Technically, it is difficult to 'circumcise' the Hartmann's pouch as described without spillage of gallbladder contents. Suppurative and other complications have been reported from spillages and lost stones[2,3]. To prevent this, we empty the stones into a retrieval bag first, rather than painstakingly fishing them out with a spoon as the authors suggest as this may result in incomplete retrieval. We also prefer to decompress a distended or an empyematous gallbladder and close the cholecystotomy before resection. In suspicious circumstances it is wise to do a frozen section as conversion to radical open surgery may be necessary. These manoeuvres add to the operating time.

Finally, the authors' claim that LSC 'has an acceptably low morbidity' is not borne out by the data: six patients had local and nine had respiratory complications, i.e. a total of 15 of 29 (crude morbidity of 51·7 per cent). A randomized trial is clearly needed to resolve this, but the emphasis meanwhile must be to convert when it is unsafe to continue laparoscopically.

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1 Hashizume M, Sugimachi K, MacFadyen BV The clinical management and results of surgery for acute cholecystitis. *Semin Laparosc Surg* 1998, **5**: 69–80.
2 MacDonald MP, Munson JL, Sanders L, Tsao J, Buyske J. Consequence of lost gallstone. *Surg Endosc* 1997; **11**: 774–7.
3 Tekin A Mechanical small bowel obstruction secondary to spilled stones *J Laparoendosc Adv Surg Tech* 1998; **8**: 157–9.

Authors' reply

Sir

We thank Zayyan and Sellu for their interest in our article and agree that bag retrieval simplifies the collection of spilled stones. However, we emphasize that LSC (as with the open technique) is not a partial removal of the gallbladder. The small residual Hartmann's pouch is not closed but excluded by suturing or ligating the cystic duct origin. It should be stressed that in most patients subtotal cholecystectomy was performed because of difficulty in separating the posterior gallbladder wall from the liver bed and not failure to define biliary anatomy. Rather than encourage 'unwise perseverance in difficult circumstances' subtotal removal simplifies management of the difficult gallbladder and was achieved in a median operating time of 73 (range 45–130) min. Although the need for open cholecystectomy was reduced, our data show that conversion was still used when safety was in doubt. While it is correct to suggest that a randomized trial could resolve the issue, there is no evidence that an open cholecystectomy under these circumstances would entirely eliminate morbidity.

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Paediatric Surgery

J. D. Atwell (ed.).
278 × 203 mm Pp 848. Illustrated 1998.
London Arnold. £175.

The first of the six sections of this book addresses General Principles of Care and covers a range of interesting topics including antenatal diagnosis, genetic counselling, nursing the sick child in hospital and in the community, the anatomy of the infant and child, and audit. Subsequent sections are Neonatal Surgery, General Surgery of Infancy and Childhood, Paediatric Urology, Trauma, and Miscellaneous; the last of these includes plastic, cardiac and orthopaedic surgery. The chapters vary in quality, but most are well written and informative, and a few are excellent. Some chapters reflect the personal bias of their (usually) eminent author and must be read with an open mind. I was struck by the uneven emphasis given to different topics. For example, there are separate chapters each for ultrasonography, isotope renography and rupture of the urethra (important but rare in children), but shorter, cryptic chapters on thoracic injuries and burns. Solid tumours (of which only four types are covered) are allocated a single chapter which is consigned with laparoscopy to the end of the book. All chapters, except one, are well referenced, although in many the most recent reference is 1992.

The book is easy to read and is liberally illustrated. A few typographical errors have slipped through in the text and figures, but the production generally is of a high standard. The compilation of colour pictures tucked away in the transplantation chapter would have been better placed at the beginning or centre of the book, with cross-references to the text. Recent textbooks on paediatric surgery published in the UK have focused specifically on neonatal surgery and the time is ripe for a comprehensive British-based textbook of paediatric surgery. This volume has much to commend it and deserves a place on the reference shelves of every medical library, but it does not have the breadth and consistent depth required of a textbook for trainees.

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Surgical Management of Abdominal Wall Hernias

M. Kurzer, A. E. Kark, G. E. Wantz (eds).
252 × 192 mm Pp. 260 Illustrated 1998.
London: Martin Dunitz. £49 95

Interest in hernia surgery has grown enormously over the past few years and an International Conference on Hernia Surgery hosted in London in 1996 has resulted in this book. The editors have assembled an impressive group of contributors and all surgeons interested in hernia repair will find something of interest. The book is well laid out with good use of tables, and clear line diagrams and black and white photographs (there are no colour illustrations). The chapter by Rutkow and Robbins on the mesh plug repair is of particular topical interest as this technique is growing in popularity. However, the title of the book is misleading; it is principally concerned with groin hernia in adults. There is no mention of hernia in babies and children, and the treatment of umbilical, epigastric, Spigelian, lumbar and parastomal hernias is not covered at all. I was surprised to read a whole chapter on groin disruption in sportsmen, especially since Jeremy Gilmore clearly emphasizes that this is a 'musculotendinous injury' and not a hernia! Although I enjoyed reading this book, I think there are better ones on the market. It certainly does not succeed as a comprehensive textbook and, as a practical manual, perhaps only one or two chapters are of interest. Many with an interest in hernia will want to dip into this volume, but I think few will wish to buy it.

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Textbook of Genitourinary Surgery. 2nd ed. (two volumes)

H. N Whitfield, W. F. Hendry, R. S. Kirby and J. W. Duckett (eds).
282 × 222 mm. Pp 1578 Illustrated 1998.
Oxford. Blackwell Science £395

This international multiauthored book with 185 contributors from all over the world comprises 127 chapters. It represents an enormous effort by the four editors and is largely successful in achieving a comprehensive coverage of the principles of urology, as well as providing a sound basic coverage of subspecialty areas, whetting the appetite for more. This is quite an achievement as urology is a specialty now in rapid evolution and, although up-to-date information covering the length and breadth of the specialty is a prerequisite, it is not easy to come by in so compact a text. The chapters are generally easy to read but it is the illustrations, in particular, that are models of clarity. There are some minor problems, including occasional duplication (common to all of these kinds of project) and a relative paucity of references after 1993 (and no easily identifiable references after 1996), which is somewhat disappointing for a 1998 edition. But this is quibbling. Overall, the text represents a very useful reference which I feel broadly defines the knowledge base required for the FRCS (Urol) and the FEBU examinations, as well as providing a readable generalist text for practising senior urologists. It would be a welcome addition to any library.

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Scientific Surgery

The British Journal of Surgery is committed to practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English language publications. A collection of all these papers will be available in the Scientific Surgery Archive which will be held on *The British Journal of Surgery* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Randomized trials

Greenway BA. Effect of flutamide on survival in patients with pancreatic cancer: results of a prospective, randomised, double blind, placebo controlled trial. *BMJ* 1998; **316**: 1935–8.

Some 49 patients were included. Flutamide, an androgen receptor blocker, improved median survival from 4 to 8 months.

Walker S, Tennant S, McSweeney ST. A randomized double-blind, placebo-controlled, crossover study to assess the immediate effect of sublingual glyceryl trinitrate on the ankle brachial index, claudication and maximum walking distance of patients with intermittent claudication. *J Vasc Surg* 1998; **28**: 895–900.

This study included 49 patients in a crossover design. A single dose of sublingual glyceryl trinitrate significantly reduced the fall in ankle : brachial pressure index after exercise (0·29 *versus* 0·36) and increased maximum walking distance (125 *versus* 105 metres).

Ibrahim S, Tsang C, Lee YC, Eu KW, Seow-Choen F. Prospective, randomized trial comparing pain and complications between diathermy and scissors for closed hemorrhoidectomy. *Dis Colon Rectum* 1998; **41**: 1418–20.

Some 91 patients were studied. Diathermy excision was associated with slightly higher pethidine requirements on the day after operation, but fewer oral analgesics thereafter. Other outcomes were similar.

Barnett HJM, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB *et al*. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *NEJ Med* 1998; **339**: 1415–25.

More results from the NASCET study. 2226 patients with less than 70 per cent symptomatic stenosis were randomly allocated to carotid endarterectomy or best medical therapy. For stenosis of 50–70 per cent, surgery reduced ipsilateral stroke by 5 years from 22·2 to 15·7 per cent. Corresponding figures for stenosis of less than 50 per cent were 18·7 and 14·9 per cent.

Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. *JAMA* 1998; **280**: 2013–9.

Some 26 randomized trials including 2211 patients were analysed. Total parenteral nutrition did not influence mortality in surgical or critically ill patients. It may reduce complication rates, particularly in malnourished patients.

Keulemans Y, Eshuis J, de Haes H, Th de Wit L, Gouma DJ. Laparoscopic cholecystectomy: day care *versus* clinical observation. *Ann Surg* 1998; **228**: 734–40.

Eighty patients were studied: 34 of 37 randomized to day care were discharged successfully. No major complications were noted and all other outcome measures were similar in each group.

Mathias L, Miller H-H, Schramm H, Gassel H-J, Rau H-G, Ridwelski *et al*. Randomized trial of surgery *versus* surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folinic acid for liver metastases of colorectal cancer. *Ann Surg* 1998; **228**: 756–62.

This was a multicentre study of 226 patients. At planned interim analysis, median survival was 34·5 months after adjuvant therapy *versus* 40·8 months in controls. the study was terminated early.

Izbicki JR, Bloechle C, Broering DC, Knoefel WT, Kuechler T, Broelsch CE. Extended drainage *versus* resection in surgery for pancreatitis: a prospective randomized trial comparing the longitudinal pancreaticojejunostomy combined with local pancreatic head excision with the pylorus preserving pancreatoduodenectomy. *Ann Surg* 1998; **228**: 771–9.

Randomization included 61 patients. One patient died after extended drainage but in-hospital complications were fewer (19 *versus* 53 per cent). Pain relief was similar but global quality of life improved more (71 per cent *versus* 43 per cent, *P* < 0·01) after extended drainage.

Tyburski JG, Wilson RF, Warsow KM, McCreadie S. A trial of ciprofloxacin and metronidazole *versus* gentamicin and metronidazole for penetrating abdominal trauma. *Arch Surg* 1998; **133**: 1289–97.

The incidence of postoperative infection (15 per cent after gentamicin *versus* 20 per cent after ciprofloxacin) was similar in this study of 84 patients.

Gilly FN, Francois Y, Sayag-Beaujard AC, Glehen O, Brachet A, Vignal J. Prevention of lymphorrhea by means of fibrin glue after axillary lymphadenectomy in breast cancer: prospective randomized trial. *Eur Surg Res* 1998; **30**: 439–43.

Some 108 patients were included, 2 ml fibrin glue applied to the axillary dissection site halved postoperative drainage by day 6 (214 *versus* 408 ml, *P* = 0·001) and reduced mean hospital stay (8 *versus* 10 days, *P* = 0·006). There was one late seroma in each group.

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